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# British Journal of Obstetrics and Gynaecology

Edited by Geoffrey Chamberlain

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SUPER ARDUA

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P, 25, 396

# 6 reasons why more doctors prescribe Prempak-C and Premarin than any other HRT.

## 50 YEARS EXPERIENCE

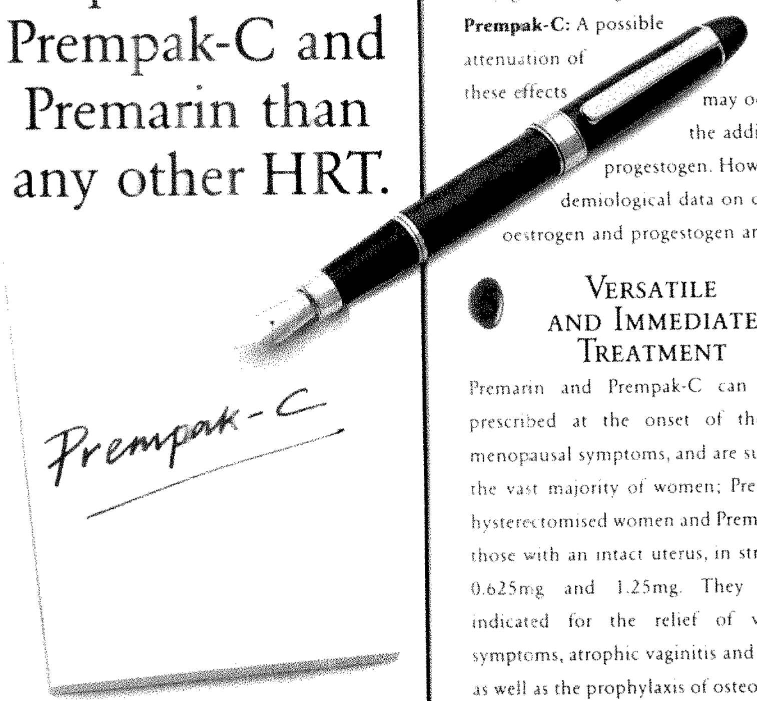
Premarin, a natural conjugated oestrogen, which is also used in the formulation of Prempak-C, is the only oestrogen used in any HRT with 50 years experience. The majority of long term studies, therefore, relate to the conjugated oestrogen found only in these products.

## LONG TERM SAFETY - BREAST CANCER?

Both doctors and patients are justifiably concerned about the potential risks of breast cancer for women taking HRT. Whilst there is suggestive evidence of a small increased risk of breast cancer with long-term HRT (greater than 5 years), this varies with the type and dose of the oestrogen used. However, a recent comprehensive review of 31 studies provides evidence that menopausal therapy consisting of 0.625mg/day of conjugated oestrogens does not increase the risk of breast cancer.[1] Most studies, in fact, relate to conjugated oestrogen and so there is insufficient data to arrive at similar conclusions for any other regimen.

## PROPHYLAXIS OF OSTEOPOROSIS

Prempak-C and Premarin are both indicated for the prophylaxis of osteoporosis in women at risk of developing fractures. A minimum daily dose of 0.625mg Premarin preserves bone mass, therefore reducing the risk of debilitating injuries such as hip fractures, by up to 66%.[2,3] Further estimates suggest that prescribing Premarin for at least 10 years will reduce the risk of mortality linked to osteoporosis by 60%.[4]



## REDUCING CARDIOVASCULAR DISEASE RISKS

**Premarin:** A recent review of considerable epidemiological evidence has shown, overall, a 50% reduction in risk of coronary disease in oestrogen users. The most common form of oestrogen used in all these studies was conjugated oestrogen, i.e. Premarin.

**Prempak-C:** A possible attenuation of these effects may occur wit the addition of a progestogen. However, epidemiological data on combined oestrogen and progestogen are limited.

PREMPAK-C
PREMARIN

## VERSATILE AND IMMEDIATE TREATMENT

Premarin and Prempak-C can both be prescribed at the onset of the earlies menopausal symptoms, and are suitable f the vast majority of women; Premarin hysterectomised women and Prempak-C those with an intact uterus, in strengths 0.625mg and 1.25mg. They are als indicated for the relief of vasomotc symptoms, atrophic vaginitis and urethrit as well as the prophylaxis of osteoporosis women at risk.

## COST EFFECTIVE

Treatment costs are becoming increasir important, especially as long term ther can last from 5 to 10 years or lon Compared to other forms of HRT, Wyet products cost remarkably little; Prema costs just £1.84 and Prempak-C costs £4. for 28 days of therapy.[7]

## ABBREVIATED PRESCRIBING INFORMATION

**PREMARIN** **USES:** Menopausal and post menopausal oestrogen therapy in women without a uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures.
**DOSAGE AND ADMINISTRATION:** Natural conjugated oestrogens 0.625mg - 1.25mg daily. Continuous administration is recommended. In women with an intact uterus the addition of a progestogen for 10-12 days per cycle is essential.
**CONTRA-INDICATIONS:** Known or suspected pregnancy and during lactation. History of known or suspected cancer of the breast. Oestrogen dependent neoplasia. Undiagnosed abnormal genital bleeding. Active thrombophlebitis or thromboembolic disorders. Acute or chronic liver disease Rotor or Dubin-Johnson syndrome. Severe cardiac or renal disease.
**WARNINGS AND PRECAUTIONS:** Some studies have reported a small increased risk of breast cancer in long term oestrogen replacement therapy users (greater than 5 years), others however have not shown this relationship. It is not known whether concurrent progestogen influences this risk. The risk of endometrial hyperplasia and carcinoma with unopposed oestrogen use is lowered by the addition of a progestogen. Diseases that may deteriorate during therapy include otosclerosis, multiple sclerosis, systemic lupus erythematosis, porphyria, melanoma, epilepsy, migraine and asthma. Use with caution in patients with pre-existing uterine fibroids, endometriosis, breast nodules, fibrocystic disease, and in those with a history of deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, cardiac or renal dysfunction. Discontinue if jaundice, migraine visual disturbances, thromboembolic phenomena or significant hypertension develop. Certain endocrine and liver function tests may be affected. Rarely idiosyncratic hypertension may occur. Discontinue treatment prior to surgery or prolonged immobilisation. Gallbladder disease. Insulin requirements may be altered. Premarin is not an oral contraceptive.
**SIDE EFFECTS:** The following have been reported with oestrogen therapy: premenstrual-like syndrome, increase in size of uterine fibromyomata, vaginal candidiasis, changes in cervical erosion and secretion, cystitis-like syndrome, breast changes, gastrointes- symptoms, chloasma, melasma, erythema multiforme, erythema nodosum, haemorrhagic erup alopecia, hirsutism, steepening of corneal curvature, intolerance to contact lenses, heada migraine, dizziness, mental depression, chorea, weight changes, reduced carbohydrate toler aggravation of porphyria, oedema, changes in libido, leg cramps.
**PRODUCT LICENCE NUMBERS:** Premarin 0.625mg PL0011/0165 Premarin 1.25mg PL0011/ Premarin 2.5mg PL0011/0167. **BASIC NHS PRICE:** Premarin 0.625mg £1.84 (28 days). Fo prescribing information please refer to data sheet.

**PREMARIN***
(Conjugated Oestrogens)

**PREMPAK-C** **USES:** Menopausal and postmenopausal oestrogen therapy for women w intact uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis v atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fracture
**DOSAGE AND ADMINISTRATION:** Natural conjugated oestrogens 0.625mg - 1.25mg daily at norgestrel 0.15mg tablet should be taken daily from day 17 to day 28 of oestrogen therapy.
**CONTRA-INDICATIONS:** As for Premarin.
**WARNINGS AND PRECAUTIONS:** As for Premarin. Prempak-C is not an oral contraceptive
**SIDE EFFECTS:** As for Premarin. Breakthrough bleeding and spotting. Change in menstru dysmenorrhoea, amenorrhoea.
**PRODUCT LICENCE NUMBERS:** Prempak-C 0.625mg PL0011/0161 Prempak-C 1.25mg PL001
**BASIC NHS PRICE:** £4.06 - 28 days. For full prescribing information please refer to data she
**REFERENCES** 1 Dupont W.D and Page D.L. (1991) Arch. Int. Med. 151, 67-72. 2 Lindsay (1984) Obstet. Gynecol. 63, 759-763. 3 Kiel D.P. et al. (1987) NEJM, 317, 1169-1174. 4 Ross R. (1989) Lancet, 1, 505. 5 Stampfer M.J. and Colditz G. A. (1991) Prev. Med. 20, 47-63. 6 Stampfer M.J. et al. (1991) NEJM, 325, 756-762. 7 MIMs June 1992.
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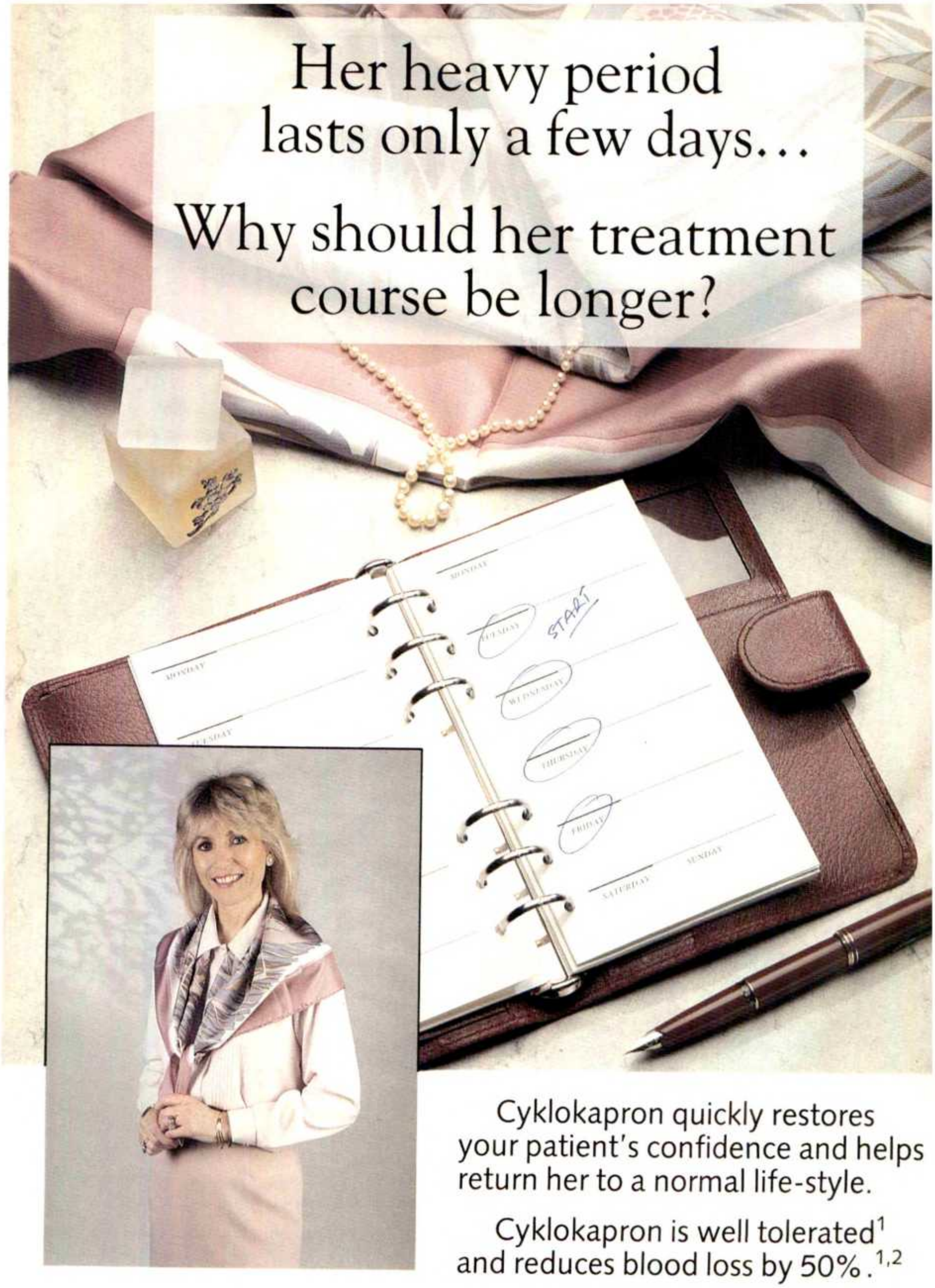

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2. Miller RM, Frank RA, Br J Obstet Gynaecol 1992; **99** (Suppl 7): 37-41

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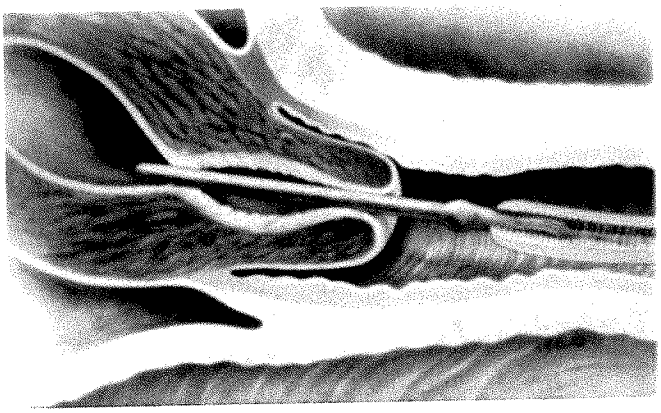

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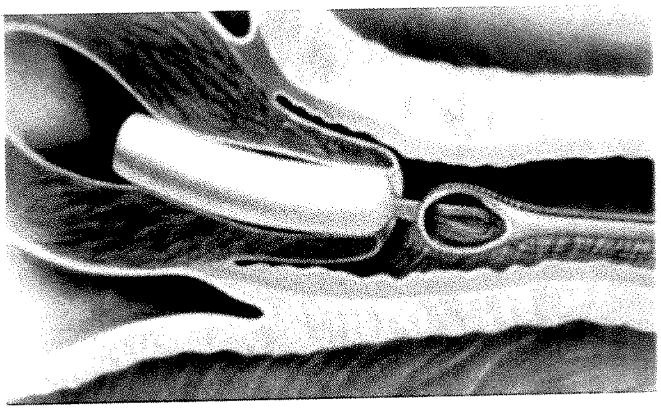

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rarely. Symptoms are normally transient. Furthermore, skin reactions have been reported. **Precautions** Physical examination and a complete medical and family history should be taken prior to the initiation of any oestrogen therapy. Patients with intact uterus who are, or have previously been, treated with unopposed oestrogens should be examined with special care in order to investigate a possible hyperstimulation of the endometrium before commencing Zumenon therapy. If abnormal or irregular bleedings occur during or shortly after therapy, diagnostic aspiration biopsy or curettage should be performed to rule out the possibility of uterine malignancy. Patients with epilepsy, migraine, diabetes, asthma or cardiac failure should be carefully controlled as oestrogens may worsen

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British Journal of Obstetrics and Gynaecology
July 1992, Vol. 99, p. 537

# A Change of Editor: Tribute to David Paintin

Contrary to the ideas of the romantic, a journal does not have a life of its own. A lot of hard work is done by contributors, referees, statisticians, sub-editors, desk editors, printers and publishers; over all of this is the influence of the editor who both drives and checks the whole process. This person must have tactical skills in dealing with individual papers and people while yet being able to lift his eyes above the parapet to mould the strategic future of the Journal along the lines he and the advising editorial board have planned.

Recently the editors of this Journal have changed. Dr David Paintin demitted office and Professor Geoffrey Chamberlain has taken over from this issue. Dr Paintin himself had assumed office from Professor Frank Hytten four years ago. A physiologist passed the direction to a social obstetrician. Such were the characters of the two men that a seamless weld allowed the Journal to go on undisturbed. Paintin (1989) displayed his credo on what the Journal would like to publish as a priority, the results of properly conducted investigations, leaving more general postgraduate education to the review journals. Properly planned clinical trials and observational research in the physiology of human reproduction were published along with descriptions of current physical practice, case reports, reviews of the subjects of educational value and occasional papers of historical interest. David Paintin is a straight thinker and stuck to these editorial principles so the *British Journal of Obstetrics and Gynaecology* flourished under his editorship, assuming a more important place in the English speaking obstetrical world. Citation index figures and new subscriptions both increased markedly, the Journal became required reading of British obstetricians and those who have been trained in the British mould.

David Paintin was a man before his time. Always intersted in the whole spectrum of reproductive physiology and pathology, he wanted to put this into the proper context for womankind. He is a social obstetrician in the pattern of Sir Dougal Baird. Dr Paintin advised the proposers of the 1968 Abortion Act and helped to defend it again in 1991. At the Royal College of Obstetricians and Gynaecologists he had a large part to play in the Report on Unplanned Pregnancy which caused such a stir on publication last year. He advised Presidents on many matters to do with abortion and family planning. He goes back to work in these fields after leaving the Journal.

All these major social issues did not alter the course of the Journal. It continued as the major showpiece of British and European Obstetric and Gynaecological research. Accepted articles were meticulously refereed and statistically groomed by a team of workers gathered and cared for by the editor. An increasing number of commentaries reflected Dr Paintin's special interests and that is how it should be.

Along with the editor's departure, the Journal office loses the services of Mrs Sonja Chayen who has stage managed the smooth running of the Journal since July 1975. As editorial assistant, Sonja has overseen the mechanics of every Journal produced, sub-editing and assembling material for the interchange with the publishers. Mrs Chayen has worked with four editors from Sir Stanley Clayton and knew more about the Journal than anyone else. We shall miss her and Valerie Bolton who supervised special aspects of the Journal such as book reviews and correspondence.

The new editor is very conscious of the continuum of the ethos of the Journal going back to 1902 when it was the *Journal of Obstetricians and Gynaecologists of the British Empire*. In 1968 it became the *Journal of Obstetricians and Gynaecologists of the Commonwealth* commensurate with changes in the world and again in 1975 it changed to the *British Journal of Obstetrics and Gynaecology*. Through this time, the Journal has continued to lead and reflect enormous changes in the subject. Starting with mainly observational studies, it brought in biochemical research as soon as that became an important area; this was followed by biophysical research and now epidemiology has become a required partner; sociology will follow afoot. With his new editorial team of Mrs Allison Richens and Miss Jayne Marchant, Professor Chamberlain hopes to build on the solid reputation that the Journal already has. Volume 100 will be published next year and that will provide a suitable time for looking back over this century and an assessment of the future. We shall miss David Paintin's quiet and firm authority, his short but well turned sentences and his commitment to the Journal. The College, the Editorial Board and the incoming editor all thank him for what he did.
G.V.P.C.

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British Journal of Obstetrics and Gynaecology
July 1992, Vol. 99, pp. 538–546

## COMMENTARIES

# Recruitment in obstetrics and gynaecology. RCOG sets initiatives

The suspicions that there are serious recruitment and retention problems in obstetrics and gynaecology have recently received much attention, suggested reasons include domestic difficulties, disillusionment with the discipline, long working hours, length of training, medico-legal implications and anxiety about job opportunities.

Before a sophisticated solution to the problem is devised the question needs to be asked 'Does the problem exist?' In 1988 a survey was undertaken by the Royal College of Obstetricians and Gynaecologists of all the UK and Eire graduates who were resident in the UK and had passed the MRCOG Part 2 examination in the 5 years 1978–1982, a total of 319. By the time of the survey (6–11 years after passing the examination) only two-thirds were consultants or senior registrars. To establish what had happened to the remaining third, a questionnaire was sent to the remaining 319 and over 60% responded.

Of the third who were not consultants or senior registrars 75% had left the specialty by 3 years after the examination. The results of a further survey of UK graduates who passed the MRCOG Part 1 examination in the 4 years 1975–1978 and who did not pass, or did not sit, the Part 2 examination showed that one-fifth had decided against a consultant career in obstetrics and gynaecology, and 86% did not attempt the Part 2. Two-thirds had left the specialty 1 year after passing Part 1.

Prompted by these depressing figures a survey was conducted on behalf of the RCOG in an attempt to ascertain why individuals choose a career in obstetrics and gynaecology, what the dissatisfactions are, what if anything would encourage trainees to stay and what external factors constrained decision-making. A total of 134 medical students and postgraduates at varying stages of training were interviewed to obtain their views on the factors influencing the decisions.

A tentative choice of career was made quite early in undergraduate training and a quarter of the group had provisionally decided which career to adopt. Pre-clinical students were thirsty for knowledge about the specialty but very critical of the lack of response to questions about career prospects. A worrying aspect of recruitment was observed in senior students after their obstetric and gynaecological attachment, as 70% of those who had admitted to enjoying the course did not pursue a career in obstetrics and gynaecology, mainly due to lack of enthusiastic follow-up by teachers and concerns passed on by junior hospital doctors about long working hours, resident conditions and job prospects.

Inadequate information and career guidance were the most important themes and applied to school leavers through medical school and postgraduate training. It seems that the young student and doctor is receptive but baffled by choices and rushed into decisions without knowledge of where to turn for advice or career planning. This echoes the views of Allen (1986).

Common anxieties of the advanced trainees included the length of training in order to achieve consultant status and the perception of being a consultant, with quality of life and adequate time off being more important than financial reward. Many of today's young doctors are not prepared to spend 11 years in training with the inevitable domestic, personal and financial disruption.

Eventually 90% of male doctors and almost as many women marry and, of those who marry, nearly 70% do so within 5 years of qualification and it is this background of personal uncertainty that is a prime influence in maintaining enthusiasm (Richards 1990).

Senior colleagues, remembering long periods of residency and years of training, may justifiably ask whether a reduction in the level of exposure to clinical work together with a 1 in 3 or even 1 in 4 nights on duty will provide adequate practical experience. Certainly future training should be different and more in line with the USA experience where licence for independent practice is usually achieved by the age of 34 following a more structured approach with mandatory continuing medical education after specialist accreditation, Saunders (1992).

An adequate assessment of the effect of litigation on recruitment could not be assessed by the survey. However, the responses suggest that medico-legal problems play a less important role in career choice than expected, though the apprehension of personal emotional trauma seems to be influencing students and doctors throughout their training periods. Clements (1991) has suggested that the present system of provision of obstetric care in the UK may have led to a litigious environment that promotes defensive medicine and encourages clinical interference for the benefit of the doctors and not the patient. This has been the subject of a detailed study by Ennis, *et al.* (1991).

In a recent questionnaire circulated by the RCOG to more than 1000 Fellows and Members 85% admitted to being involved currently in litigation, or having been involved, during the previous 10 years and that this had not only an effect on recruitment but on plans for their age of retirement. Even if the present 'Tort' system is revised or replaced by a no-fault compensation scheme the problem of medical malpractice will not go away and sensible and sensitive practice, together with support from experienced professionals, must be encouraged (Chamberlain & Orr 1990). Equally important is the need for continued research into the aetiology of birth asphyxia and cerebral palsy, not only to prevent their occurrence but also to provide the lawyers with facts on which to base their deliberations.

Women at present hold 14·7% of all consultant posts, a lower figure than might be expected, in view of the appreciably higher proportion of women who qualify in medicine. Overall 12.2% of consultants in obstetrics and gynaecology are women and the proportion has been creeping up slowly. Over 50% of graduates qualifying next year will be women and special consideration needs to be given to their problem. According to Blunt (1990), the issue is complex and some of the reasons for women leaving hospital work are the same as for men. However, the difficulties of combining marriage and children with a rigid postgraduate training programme was quoted as the commonest reason for women leaving the specialty and the RCOG recognizes the need for increasing the number of re-entry and retraining schemes, part-time appointments and job-sharing possibilities.

The study confirms the suspicions that there are serious recruitment and retention problems in obstetrics and gynaecology. The attractions of the subject at student level are diminished by the time of qualification and the pre-registration year, leading to a change of career choice. It appears that the young doctor of the 1990s is not prepared to sacrifice domestic involvement and financial security during the lengthy training period and that quality of life has an important influence on career choice.

So what can be done to make obstetrics and gynaecology more attractive? From the recruitment aspect, the College has set up a study group to address the problem of recruitment and wastage, to advise on the role of the College in the promotion and maintenance of recruitment in the future, and to suggest ways of highlighting public awareness of the specialty. The report of the group will be presented to Council shortly.

The College has for some time been active in reviewing current postgraduate activities and has recognized the importance of the regular reassessment of an individual's professional skills. The Peel Report on Continuing Medical Education has been approved by Council and its recommendations of mandatory further education and, possibly, recertification of specialist accreditation are logical, if the years of training are reduced and the average age of attaining consultant status is lowered to a realistic level.

The implications of the involvement of trainees in research projects (Howe 1992) and the vexed question of a second postgraduate qualification (Studd 1992) are matters that need addressing. The College recognizes that trainees are seeking official guidance in these areas.

The stress experienced by juniors can be alleviated only by marked changes in current practice—the creation of residency programmes so that those selected as having career prospects have an assured sequence of posts for the whole of their training period in one part of the country—an organized academic component of postgraduate training—an acceptance of a one in four rota, with adequate time off the day following a night on duty, and a fuller sharing of the care of healthy pregnant women with the midwifery profession. Trainees who attended the hugely successful Manpower Meeting at the RCOG should have been reassured that the College is anxious to understand their problems and is willing to listen and act.

A Working Party that will advise on structured training has already been commissioned, and the College is aware that the quality of training has an important part to play in attracting candidates of a high calibre to obstetrics and gynaecology. This was demonstrated by the general practitioners who were the first to revolutionize their training style, with a resultant rise in a number of good recruits to general practice (Chapple 1991).

But what of those responsible for training? Over the past few years there has been a plethora of documents referring to the need to develop a coherent structure to inform, advise and appraise hospital doctors in the training grades. These have arisen partly as a consequence of 'Achieving a Balance' (DHSS Publication 1988) and partly from a realization that any reasonable training structure requires the counselling of trainees. Much has already been done to improve advice given to juniors by College tutors, clinical tutors, and individual consultants. However, it appears that trainees make poor use of these sources of support, mainly because their use is voluntary and access is not organized. There is an urgent need to coordinate the efforts of all these bodies and to make counselling and career guidance individual and mandatory. This necessarily involves a high degree of enthusiasm and commitment by trainers.

The major changes already underway will inevitably take time to implement but the unparalleled efforts by the RCOG to revitalize the specialty are already paying dividends.

The number of UK graduates in career SHO posts has increased sharply, there are more female senior registrars than ever before and there is a significant downward trend in the number of deliveries managed by each consultant (RCOG Manpower Report 1992). Equally encouraging is an awareness by delegates attending the recent Manpower Conference at the RCOG that the College is determined to lead and support its trainees.

Finally, the College is applying pressure on the Government to accept the need for increasing the number of consultant posts and to lessen the demands on junior staff. Without this our junior colleagues may not achieve an improvement in the quality of their lives, and the College will not succeed in its aim of safeguarding the interests of patients.

Those holding the purse strings must be made to realize that training involves not only achieving clinical expertise, but also acquiring the time and ability to listen, communicate, teach, conduct research, and manage budgets and people. The attainment of these other skills is time-consuming and costly but is essential if the specialists of the future are to be competent sympathetic doctors.

**Peter Saunders**
*Consultant Obstetrician & Gynaecologist*
*Ashford Hospital, Middlesex*
*Chairman, Recruitment Study Group, RCOG*

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July 1992, Vol. 99, pp. 540–543

# Measuring maternal mortality

Measuring maternal mortality is extremely difficult. Different approaches have varying degrees of success and each method has advantages and shortcomings. Techniques from related fields such as infant mortality are unsuited to measuring maternal mortality. Researchers, insufficiently familiar with the problems, have wasted much time, effort and money only to obtain information of questionable scientific value.

Most official measures of maternal mortality are underestimates. The reasons for this vary according to certification practices and the degree of sophistication of the vital registration system. Although the definition of a maternal death in the International Classification of Diseases (ICD 9 and 10) is scientifically incontrovertible, in practice maternal deaths often escape being so classified because the precise cause of death cannot be given even though the fact of the woman having been pregnant is known. Cause of death is routinely reported for only 35% of the world's population. To facilitate the identification of maternal deaths, the ICD 10 has introduced a new category, that of 'pregnancy-related death', which is intended for use in countries that wish to count maternal deaths, but where the cause of death cannot be identified precisely. This will, however, require that all death certificates include a question on pregnancy status of the deceased woman (Fortney 1990). Only a few countries do so at present.

Where good vital registration does exist, biases are usually due to incorrect classification of the cause of death. There are many social, religious, emotional or practical reasons for not classifying a maternal death as such, especially if it relates to abortion.

In most developed countries and in most hospital settings all over the world there is usually an inquiry following a maternal death. This may constitute an incentive to attribute a maternal death to a less blameworthy cause. Such misrepresentation may not be very common in countries with a tradition of 'no name, no blame' confidential inquiries, but appears to be quite common elsewhere (Royston & Armstrong 1989).

Where maternal mortality is low, few maternal deaths actually take place in obstetric departments of large hospitals, because when life-threatening conditions arise the patient is transferred to another specialist department. The death will not be certified by an obstetrician and the cause of death appearing on the certificate may well not mention the obstetric condition which triggered the fatal sequence of events. A recent enquiry in France (Bouvier-Colle *et al.* 1991) has brought to light that one third of the 41 deaths reported as being related to maternal conditions by the certifying doctor were subsequently miscoded by the coding clerks. For example, cerebral haemorrhages were classified in 'Diseases of the circulatory system' instead of 'Complications of pregnancy, childbirth and the puerperium'.

Even in countries where all or most deaths are medically certified, maternity-related mortality can still be grossly underestimated. Record linking and other studies have shown misreporting of between 25% (Smith *et al.* 1984) and 70% (Morbidity and Mortality Weekly Report 1991) of maternal deaths in the USA. The French study found 56% under-reporting. The situation is even worse where the registration of the fact of death is complete for deaths but poor for the cause of death. Maternal mortality measures based on such data are extremely misleading. It is clear that even in the most favourable circumstances special efforts have to be made—and additional costs incurred—to get good data on maternal mortality.

Where civil registration is incomplete, or nonexistent, other sources of information must be used. There is a hierarchy of situations ranging from countries like Bangladesh, where 95% of the births are attended by untrained traditional birth attendants or relatives and no civil registration exists, through countries like Brazil with 75% coverage of civil registration and India, with a 1% sample registration system. The choice of method for identifying maternal deaths will depend not only on circumstances but also on the purposes for which the data are to be used. Are they to be used for monitoring over time? Or for planning health services and infrastructure? Or for determining health care priorities? In each case the degree of precision has to be balanced against the cost in money and human resources.

### *Maternal mortality rate*

The maternal mortality rate (Fortney 1990), the most commonly used indicator of maternal death, measures a woman's chances of dying from a given pregnancy and should, theoretically, relate the number of maternal deaths (as the numerator) to the total number of pregnancies (as the denominator). The numerator should include all deaths defined as 'maternal deaths' (e.g., including deaths from ectopic pregnancy) in a given time interval, and the denominator all episodes of pregnancy occurring in the same time interval, regardless of their outcome. In practice the population at risk of a maternal death is generally taken to be the number of live births which is assumed to be a good proxy indicator of the number of pregnancies. The rate is usually expressed as per 100 000 live births. (In accordance with the ICD definition, we have used the term maternal mortality rate to describe the ratio of maternal deaths to live births. Strictly speaking this term should be called the maternal mortality ratio.)

### *Community surveys*

Maternal mortality can be measured by incorporating questions on maternal deaths into on-going (large-scale) household inquiries. It is possible to ask questions on pregnancy status and to make a repeat visit one year later to ascertain the pregnancy outcome. Alternatively, retrospective questions can be asked about household members. A community survey in Addis Ababa was based on a sample of households to identify births, abortions and deaths over a defined period of time (Kwast *et al.* 1985). These were then followed up and details of care received, social and other characteristics of the women and households, as well as circumstances and causes of deaths, were recorded. In another study in Indonesia, investigators visited 150 000 households, and recorded 15 000 births to identify 50 maternal deaths (Agoestina & Soejoenoes 1989).

These figures illustrate the drawback of using household surveys, namely the expense involved. Household surveys are not a cost-effective way of measuring maternal mortality. However, it may be possible to add questions on maternal deaths on to demographic or household surveys. There are several recently developed techniques which make the most of the information so obtained.

One such is the 'sisterhood method', which asks all adult women in a household survey four simple questions about the survival of their sisters. This information is converted into lifetime chances of dying from maternal causes and hence into estimates of maternal mortality by a series of mathematical calculations (Graham *et al.* 1989). The technique has proved successful in some countries but, for reasons not yet fully understood, less so in others. The sample size required is very large and the method yields no information on the causes of the maternal deaths or of the circumstances surrounding them.

Another new technique, which is a cross between a household survey and a reproductive age mortality survey (see below) was used in Kenya where women interviewed in a child survival survey were asked whether they knew of any women who had died from maternal causes in the preceding year (Boerma & Mati 1989). This technique, known as 'networking', is promising for use in well defined geographic areas.

### *Reproductive age mortality surveys*

Perhaps the most successful and economical way of measuring the extent and causes of maternal mortality is to identify and investigate the causes of all deaths of women of reproductive age. This technique has been used successfully in countries as different as Guinea and Honduras. In the latter, the maternal mortality rate was found to be four times that based on civil registration. How the deaths are identified differs according to the records and/or the types of knowledgable informants available. All successful studies use multiple and varied sources of information—civil registers, hospitals and health centres, community leaders, schoolchildren, religious authorities, undertakers, cemetery officials, etc. No single source identifies all the deaths (Walker *et al.* 1986).

Where reasonable civil registration systems exist, death certificates alone are a useful starting point for identifying deaths of women of reproductive age. This was successful in Latin America in the 1960s and has lately been widely used elsewhere. A panel of medical specialists then establishes whether or not the death was pregnancy related from hospital records and/or from symptoms reported by the family of the deceased. Attractive as it is, this approach only works if the area under study is well defined. A pilot study in Karachi, Pakistan, found the technique unsuited to a large urban setting (Aga Khan University, personal communication). The area covered by each source of information (or informant) was impossible to delineate and there were difficulties due to women who had left the city to give birth in their home villages and/or to those who had come into the district to give birth at the city hospital.

### *Hospital data*

In the absence of civil registration or other population-based data many researchers use hospital data to estimate maternal mortality. There are limitations to this approach and estimates calculated on hospital data alone tend to be unrepresentative. Firstly, a large proportion of the women who die in hospitals are emergency admissions, women who had intended to give birth at home but who were transported to hospital when they developed a life-threatening condition. Safe deliveries at home do not of course appear in the denominator. This phenomenon emerges very clearly when hospital data are divided into booked and unbooked patients. At the Black Lion Hospital in Addis Ababa, Ethiopia, for example, the maternal mortality rate in 1980–81 was 210 for booked compared with 1050 for unbooked patients (Horvath & Muletta 1982, unpublished document).

Secondly, if a referral system is working efficiently most high-risk women are referred to the hospital for delivery. This means that among the women giving birth at the hospital there is a disproportionate number with obstetric complications, and hence of women who die there. The women who have been referred to the hospital for delivery will appear in the statistics as booked patients. It is not possible, therefore, to estimate the degree of bias introduced into the maternal mortality rate as a result. A third source of bias is that of socioeconomic selection. If a hospital is fee-paying or caters for patients with a certain type of insurance, e.g., private clinics, military hospitals, it will attract economically advantaged women. Such hospitals may have a lower maternal mortality rate than that prevailing in the community.

In general, the fewer births take place in hospital the greater the discrepancy between the true—usually unknown—population rate and the hospital rate.

Nonetheless, valuable information can be obtained from hospital studies which can shed light on avoidable factors, especially those in hospital, and suggest specific interventions. Several studies have used hospital deaths as a starting point in tracing back the path followed by the dead woman—her prenatal care, who attended the birth, problems encountered in transport, financial and social barriers to the use of services, as well as shortcomings in the health care system (Mbaye & Garenne, unpublished report 1987). Computer matching of deaths of women with births and fetal deaths and then with their hospital records in the USA has, with the help of suitable case controls, made it possible to assess treatment they received (Centers for Disease Control 1991).

Case control studies for the study of the causes of maternal deaths require a very careful matching of controls, in the absence of which the study will only show the obvious—that the cases developed complications and the controls did not—or that the cases were older, multiparous, poorer, etc. Matching with women developing similar complications but who survived would yield much more useful results.

Hospital data must be used cautiously for cause of death information. In general, emergency complications from which women die quickly (e.g., haemorrhage), will be under-represented because many women will not reach the hospital in time. A study in Bangladesh showed that only 1 of the 58 deaths identified took place in hospital, and this was from eclampsia whereas the majority of deaths at home were from haemorrhage (Khan *et al.* 1986). Deaths occurring early in pregnancy (e.g., abortions, ectopic pregnancies) may not be included because they occur in a different part of the hospital.

### *Primary care level*

Many community studies show that records at the primary care level can be used for computing infant mortality rates. Theoretically, maternal mortality rates can be calculated in the same way. But even in countries with high maternal mortality, a maternal death is a rare event and to establish a maternal mortality rate of, for example, 300, correct to within 20% (95% confidence level), would require a sample size of 50 000 births.

### *Making estimates from incomplete data*

It is sometimes necessary to make estimates of maternal mortality for geographic areas with no figures. A common error is to use only such data as exist, thereby making the implicit assumption that the missing areas (or countries) resemble those for which there are data.

The approach that we adopted to estimate regional and global trends (Weekly Epidemiological Record 1991) was to use the logistic regression curve obtained by plotting maternal mortality rates (based on good community studies or adequate registration data only) against a number of demographic and other development indicators, to estimate rates for missing countries. Needless to say, all the rates, including the dummy values so obtained, need to be weighted by the number of births or converted into the estimated number of deaths, before being added together. This type of estimate also provides a useful tool for assessing whether rates obtained from civil registers, studies or other sources are plausible.

The inconsistencies are well illustrated by data from Honduras. The official maternal mortality rate, based on civil registration, was 50 per 100 000 live births in 1983 (PAHO 1990). A nationwide RAMOS (Castellanor *et al.* 1990) study in 1989–1990 yielded an overall rate of 221; for hospital deaths only the rate was 175. The logistic regression yielded an estimate of 210.

In addition to statistical techniques one can learn a great deal using social science methods to elicit people's opinion on priority health problems. Such techniques may not yield quantitative estimates but can provide useful pointers.

Inevitably the places where maternal mortality is highest, and where there is the most urgent need for action, will also be those with the least reliable data—if any exist at all. Under such circumstances a picture has to be built up using a multiplicity of possibly unreliable sources. It thus becomes even more essential that those using the data should know exactly what can and what cannot be read from them.

A fuller discussion of these issues as well as the sources from which examples are drawn can be found in *Maternal Mortality: A Global Factbook* (AbouZahr & Royston 1991).

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# Prelabour rupture of the membranes—why hurry?

The optimum management of prelabour rupture of the membranes at, or near term, has long presented obstetricians with a dilemma. Increasingly, as methods of stimulating and controlling uterine activity have become available, there has been greater enthusiasm for intervention. The justification has mainly been fear of serious maternal or neonatal sepsis.

The effect of intervention on subsequent labour and delivery has to be assessed against other developments in obstetric care, including earlier recourse to caesarean section. There has been a dearth of carefully controlled studies in this area, but the large, randomized study reported in this issue (Grant *et al* 1992, p.557) provides encouragement for a conservative approach, at least by delaying stimulation for some hours. Waiting a while seems to reduce the likelihood of a woman requiring a section and the policy seems to be safe.

New terminology has been introduced in recent years. The term used previously of 'premature rupture of the membranes' may wrongly convey an impression of preterm labour only. 'Prelabour rupture of the membranes' (PROM) is more descriptive and precise and can be further qualified by gestational stratification.

The incidence of PROM is not clear. It has been considered to apply to as many as 20% of women at term (Johnson *et al.* 1981; Daikoku *et al.* 1982) but the proportion depends on whether women on the verge of labour at the time of membrane rupture are included. The accuracy of diagnosis of rupture of the membranes is another variable that will affect the apparent incidence. The clinical problem relates to women where there is a latent period before the start of uterine activity. A duration of at least 1 h has been suggested in the past (Burchell 1964) and on this basis, the incidence at term appears to be 6-12% (Russell & Anderson 1962; Rovinski & Shapiro 1968). The real clinical problem relates to fewer women than this, since time before admission to hospital and for assessment is usually longer than 1 h. The criterion of absence of contractions for one hour of observation after admission, used by Grant *et al.* (1992) seems reasonable.

Most women at term will go into labour spontaneously if left alone after membrane rupture, although about 15–20% will not do so within 24 h (Kappy *et al* 1979) and even after 7 days about 3% remain undelivered (Kappy *et al.* 1982). Altogether, about 2–4% of term births will be complicated by PROM where labour does not occur spontaneously for at least 24 h (Rovinski & Shapiro 1968; Daikoku *et al* 1982; Schutte *et al.* 1983).

Evidence concerning the risk of maternal or fetal infection is lacking in present day conditions. It probably varies with the population and seems to have changed over time. Older papers reported a seemingly inexorable rise in perinatal mortality as the latent period after membrane rupture increased (Lanier *et al.* 1965; Rovinski & Shapiro 1968). However, there are other factors. Preterm pregnancies were often not considered separately. Such pregnancies are more liable to a longer latent period and the babies are (or certainly were) less likely to survive because of their immaturity. It is also likely that infection is more often the primary cause of preterm rather than term PROM. Again, some of the perinatal mortality after PROM is due to obstetric factors e.g., cord prolapse (Taylor *et al.* 1961). Maternal death from sepsis after PROM is recognised (Russell & Anderson, 1962) and the possibility of serious sepsis prevents a widespread policy of home care at term after membrane rupture except with very close observation and opportunity to intervene with antibiotics in the presence of positive features. As Grant and colleagues note, it would require a very large study to detect any difference in infection rate between any two management policies. Thus, it is the advisability and yet the unacceptability of prolonged hospital stay which drives the urge to hasten delivery.

Such intervention is not free of complications. Early use of intravenous oxytocin seems to be associated with an increase in the rate of caesarean section, due either to failure to promote satisfactory labour or to fetal distress. (For discussion and references, see Grant & Keirse, 1989). This section rate can vary from 3 to 47% with many variables accounting for this inconsistency. Some studies have been based on very small numbers (Magos, *et al.* 1983; Ekman-Ordeberg, *et al.* 1985) and some were of mixed parity (Lange *et al.* 1981; Duff *et al.* 1984). The very high rate of 47% (Kappy *et al.* 1979) seemed to be associated with very early recourse to section. Some authors started oxytocin within 4–6 h (Magos *et al.* 1983, Lange *et al.* 1981) while others waited for 12 h (Duff *et al.* 1984). Section rates of 15–20% (Turner & Macaulay 1986;

Duff *et al.* 1984) in nulliparous women, seem to be representative and the study by Grant *et al.* (1992, p. 557) is consistent with this. Of their 219 women given oxytocin early, 17% were delivered by section.

Waiting for at least 12 h will result in a lower rate of section (11% in the study described) and more spontaneous births. This seems a good bargain. Previous open studies have provided similar section rates (Conway *et al.* 1984) without evident sepsis. There are other advantages. The women in the Lanarkshire study who had delay before stimulation required less analgesia and fewer had an intravenous infusion. If delay of a number of hours before stimulation is good, could waiting longer be better? The median time in this study was 12 h but there is suggestive evidence that those who waited longer did better. Open-ended antenatal admission is not popular with women but these figures refer to primigravidae and many may consider that waiting is acceptable if there is definite gain.

Of course, other methods of stimulation have been tried. Vaginal prostaglandins to shorten the latent period are of current interest. Earlier reports of vaginal prostaglandins in PROM have not provided a convincing answer. A randomized study of prostaglandin gel compared with intravenous oxytocin included only 10 women in each group (Ekman-Ordeberg *et al.* 1985). Another randomized study with 36 women comparing vaginal prostaglandin tablets with intravenous oxytocin included different parties (Magos *et al.* 1983). In an open study (Macauley *et al.* 1989) of 100 nulliparous women with a low Bishop score given prostaglandin tablets vaginally, there was a section rate of 7% This seems promising but it was not a controlled trial. In a recent study (Mahmood *et al.* 1992) women were randomized to receive prostaglandin gel or to wait. Both groups were given oxytocin to accelerate or, if necessary, to induce labour by 24 h from the PROM. There was no difference in the section rate and the only demonstrated benefit was a reduction of 5 h in the median time from PROM to delivery in the prostaglandin treated group. Only two women (in the conservative group) of a total of 220 women in the study, were undelivered 48 h after the membrane rupture. More women were delivered within 24 h if the cervix was favourable at the time of admission. For those with an unfavourable cervix, more of the women given prostaglandins were delivered within 24 h than those treated conservatively, and it may be this subgroup who have most to gain.

How can we summarize the current evidence? In term or near term pregnancy, with diagnosed rupture of the membranes and no evidence of infection or of obstetric hazard, there seems no need to rush. A delay of at least 12 h will allow many women to reach active labour spontaneously and their chance of a spontaneous delivery is enhanced. Thereafter, the acceptability of waiting longer, the resources required for surveillance and, above all, the wishes of the woman herself could determine the timing of intervention. The nulliparous women with an unfavourable cervix at initial assessment has most to gain by waiting. Whether she would benefit by early use of vaginal prostaglandins is unclear. Such women are comparatively uncommon in any single hospital and a well-conducted, multicentre trial would be required to provide this answer.

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# Flow cytometry

Flow cytometry, as we know it today, can be traced back to the mid-1960s. Interestingly the early machines, developed in a few industrial and university research laboratories, were all designed for important clinical applications. Attempts were made to use the method for automated cancer cytology, differential white blood cell counting and analysis of tumour cell kinetics (Traganos 1991). Difficulties in instrument design, data processing, development of fluorescent dyes, cytochemistry and sample preparation have considerably slowed the successful application of the technology to clinical material Over the past decade great advances have been made in this field: flow cytometry is now a standard technique for the analysis of circulating blood cells and for the measurement of DNA content in solid tumours (Melamed *et al.* 1990).

Flow cytometers are instruments constructed to measure and record fluorescence and light scatter. The measurements are performed on cells or other particles which are focused hydrodynamically and pass an excitation source (either a laser or mercury arc lamp) one by one in a laminer flow jet of liquid suspension medium (Koss *et al.* 1989). As the particles pass, the laser beam light is scattered in various directions. The light intensity of each particle is detected by photomultiplier tubes and converted to a digital electronic signal (Steen 1990). Some cell types, such as red blood cells, granulocytes and lymphocytes have typical light scatter characteristics. In addition to light scatter, the detectors can also measure the fluorescence of every cell. The technique can therefore be used to measure any cellular component provided that a fluorescent marker is available that reacts specifically and stoichiometrically with that constituent. If cells are stained with fluorochromes emitting light in different spectra, several cell constituents can be quantified simultaneously. High power computers are needed to analyse the data generated by flow cytometers as up to eight simultaneous measurements can be performed on 3000 cells per second. Data are represented graphically by dot plots or frequency histograms. As the presence of the compound under investigation is recorded by the cytometer in each individual cell of a sample, small subpopulations of cells can be easily identified. Computer analysis of the data allows quantification of fluorochrome binding in subpopulations of cells and calculation of the percentage of cells in subpopulations.

Flow technology is complementary to classical biochemical and immunohistochemical techniques. It can provide objective measurements of a representative sample of cells ($10^5$ or more) from a large volume of tissue more rapidly and easily than histology and image analysis or spectrometry (Baak 1987). Flow techniques are highly reproducible, accurate and sensitive: a detection limited equivalent to 150 molecules of free fluorescein per cell has been achieved (Watson & Walport 1986). Dynamic events that take only a few seconds can be studied. The technique has the unique ability of allowing simultaneous measurement of several constituents on a cell-to-cell basis. Multivariate analysis of such data yields much information on the relation between the parameters measured. The lack of visual control, the loss of structural information in solid tissues and the destructive nature of the analysis are the main drawbacks of flow cytometry. Careful sampling of tissues and (immuno)histochemical or cytochemical controls must be used to interpret the results. In addition, the hardware is very expensive and may not be generally available.

Mechanical or enzymatic tissue dissociation methods are required to make single cell or single nuclei suspensions from solid tissue samples. Disaggregated single cells or nuclei can be analysed fresh, or fixed and preserved. Only minor alterations in the quality of DNA histograms are noted in the latter situation (Coon *et al.* 1988). However, little work has been done on the effect of fixation and storage on measurements of cellular components other than DNA. Hedley *et al.* (1983) developed the first method for making nuclear suspensions from paraffin blocks. It allows retrospective flow cytometric DNA analysis and measurement of nucler proteins such as oncogene products. Excellent histological controls for the tissue taken for flow cytometry are possible by taking adjacent sections for histology and, if necessary, the cells of interest can be microdissected out. The quality of these suspensions is usually lower than that of fresh cell suspensions, and cytoplasm, plasma membrane and extracellular material are lost due to the harsh enzymatic digestion required for this tissue dissociation method (Hedley 1989). Despite these drawbacks, the validity of studying paraffin-embedded material has been proved repeatedly by comparison with corresponding fresh tumour material.

Single parameter measurements of DNA can be accomplished with several established fluorochromes, such as ethidium bromide and propidium iodide, that bind nucleic acids specifically and stoichiometrically. As large numbers of cells are analysed, appropriate statistical methods can be applied to the resulting data to give information on DNA content and cell cycle variables. DNA histograms are usually interpreted according to guidelines provided by a convention on nomenclature for expressing abnormalities of DNA content (Hiddemann *et al.* 1984). If the main peak of the DNA histogram centres around the 2C region and the overall DNA distribution is similar to that of normal somatic cells, the tumour is classified as diploid. Populations of cells with a DNA content not equal to that of normal cells are referred to as aneuploid. Assuming that the percentage of cells synthesizing DNA (S phase cells) is a direct reflection of tumour proliferation, computer software for flow cytometric cell cycle analysis has been developed (Watson *et al* 1987). Techniques for estimating S phase fraction (SPF) cell populations are numerous and relatively simple for 'clean histograms'. However, in histograms with a high coefficient of variation (CV), high skewness of the modal peak, or high amount of cell debris, and in aneuploid tumours with several overlapping cycling cell populations, cell cycle analysis is much more complicated, often depends on the judgement of the analyst and is sometimes impossible (Koss *et al.* 1989). Multiparameter flow cytometric assays based on bromodeoxyuridine incorporation in DNA or assessment of proteins involved in the control of cell proliferation (e.g. Ki-67, PCNA/cyclin) are currently under evaluation and are likely to provide more accurate indices of cell proliferation.

In spite of the pitfalls of DNA analysis, there is good evidence from retrospective and prospective studies that DNA-based measurements of the tumour ploidy and S-phase fraction are useful independent prognostic factors in patients with carcinoma of the ovary and endometrium (van Dam *et al.* 1991). Reports on the relation between cervical carcinoma tumour DNA content and patient prognosis have been equivocal. At present, flow cytometric DNA analysis should be used with extreme caution to predict the outcome for individual patients, as other factors play an important role in determining the biological behaviour of neoplasms. Nevertheless, it has been suggested that estimations of DNA ploidy and/or S-phase fraction could be included in prospective stratification of therapeutic regimens for some tumours (e.g. borderline ovarian carcinoma).

The availability of monoclonal antibody technology and new fluorescent probes and markers provides the potential for unprecedented multiparameter flow cytometric investigations. Non-DNA cell components can be labelled stoichiometrically with fluorochromes or with antibodies labelled with fluorescent dyes. There are several potential problems associated with the use of antibodies to quantify cell constituents: tissue disaggregation, cell fixation and subsequent preservation may cause epitope loss or allosteric changes in the conformation of the antigen studied. Quantification of cytoplasmic, nuclear and intracellular antigens with antibodies is particularly difficult as it requires cell membrane permeabilization. Immunocytological or immunohistological controls and independent biochemical evidence (e.g. immunoprecipitation), together with the use of adequate positive and negative controls and peptide blocking assays, should be used to conform quantitative multiparameter flow cytometric data before accepting them as meaningful. In addition, controls are needed to adjust for nonspecific binding and trapping of the antibodies.

Several authors have studied the expression of cell surface markers, oncogenes and steroid receptors, ligand binding, dye-permeability, toxicity analysis, enzyme activity, various aspects of chemo- and radio-resistance in cultured cell lines and cell suspensions prepared from solid tumours and cervical smears by means of multiparameter flow cytometry (van Dam *et al.* 1992). The technique has the potential to play an important role in the study of carcinogenesis. With an appropriate panel of monoclonal antibodies, flow cytometry may be used for screening, 'biochemical' diagnosis of neoplasia and for rapid drug, hormone or radiotherapy sensitivity tests.

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## OBSTETRICS

# Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean

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## ABSTRACT

**Objective** To present estimates of maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean, and to discuss strategies to prevent these deaths

**Design** Retrospective review of all available data.

**Setting** Database of the World Health Organization's Maternal Health and Safe Motherhood Programme.

**Main outcome measures** Estimates of the total maternal mortality and the proportions of deaths associated with hypertensive disorders of pregnancy.

**Results** Estimates of mortality associated with hypertensive disorders of pregnancy were similar in Africa, Latin America and the Caribbean, despite considerably higher total mortality in Africa. Variations in both overall mortality and that associated with hypertensive disorders of pregnancy were greatest in Asia. Despite their limitations, these data suggest that between 10–15% of maternal deaths are associated with hypertensive disorders of pregnancy, and that 10% are associated with eclampsia.

**Conclusions** Where maternal mortality is relatively high, the excess is likely to be due to a high mortality associated with haemorrhage and infection and reductions are most likely to come from reductions in these deaths. Evidence from both developed and developing countries suggests that deaths associated with hypertensive disorders of pregnancy are the most difficult to prevent. More rigorous assessment of interventions designed to prevent these deaths is urgently required.

Over the last 10–15 years an increasing number of studies conducted in various parts of Africa, Asia, Latin America and the Caribbean, have drawn attention to an ongoing holocaust. It is now widely accepted that at least half a million women die each year of pregnancy-related causes, and that 99% of these deaths occur in the developing world (Mahler 1987; Rosenfield & Maine 1985). Put another way, women in industrialized countries have an average lifetime risk of dying from pregnancy-related causes of between 1 in 4000 and 1 in 10 000, whereas women in developing countries have a risk that is between 1 in 15 and 1 in 50. In developing countries, maternal mortality is 100–200 times higher than in Europe and North America. There is no other public health statistic for which the disparity between developed and developing countries is so wide.

Until the 1940s, infection, hypertension, and haemorrhage were the main causes of maternal mortality in western countries, accounting for more than three-quarters of all maternal deaths (Loudon 1991). Maternal mortality in developed countries has declined dramatically over the last 60 years, and is now very low. The causes of maternal deaths have also changed. Deaths from haemorrhage and deaths from infection have almost disappeared. Deaths associated with hypertension have come to occupy first place and now account for a large proportion of maternal mortality (Redman 1988), an indication that these deaths have proved to be particularly difficult to prevent.

In developing countries there are echoes of the situation which prevailed in now developed countries during the late 19th and early 20th centuries (Loudon, 1988, 1992). Haemorrhage and infection still cause a vast number of deaths which should be preventable, despite evidence that the majority of such deaths should be preventable by relatively simple procedures, without any need for high-technology hospital facilities. Less is known about the levels of mortality associated with hypertensive disorders of pregnancy, but it is plausible that they are too high.

Data on total maternal mortality in developing countries have been valuable in highlighting the scale of the problem, but rational strategies to prevent these maternal deaths depend on more information about cause-specific mortality. Social, economic, political and geographic barriers often make it difficult, or impossible, for some countries to provide the necessary basic medical care to prevent maternal deaths from infection and haemorrhage. For hypertensive disorders, however, the

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problems are even more difficult. The purpose of this paper, is to describe the mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America, and the Caribbean, and to discuss the implications for possible strategies to reduce these deaths.

## Materials and methods

The World Health Organization's Maternal Health and Safe Motherhood programme has, for many years, gathered information on maternal mortality and morbidity. The information comes from a wide variety of sources, including government statistics, health service and hospital records, research results, journal articles, consultants' reports, doctoral and other theses, and, from individuals, agencies and organizations. This database has recently been used to compile a country-by-country survey of maternal mortality and morbidity (AbouZahr & Royston 1991).

Data presented in this paper were obtained by searching the WHO database for information on total maternal mortality, and on deaths associated with hypertensive disorders of pregnancy. Wherever possible this was done by referring to the original source documents. For Africa, the search was conducted during April 1990, for Latin America and the Caribbean during June 1990, and for Asia during November 1990. Each data source was classified as being either community-based, or from other sources. Most of these other sources were hospitals, but some were vital events registration, or government estimates. The methods used to measure maternal mortality are discussed elsewhere in this issue of the Journal (Royston & AbouZahr 1992).

For each country, the numbers of community-based studies, and the maternal deaths they recorded, were compared with the corresponding numbers from other sources. Total maternal mortality was estimated using the weighted average of rates reported in all studies from that country. Studies completed before 1960 were excluded, as were studies which did not estimate both a numerator and a denominator. Where cause of death data were reported, these were used to estimate the proportion of deaths due to hypertensive disorders of pregnancy, again using a weighted average.

This was multiplied by the total maternal mortality rate for that country, to give an estimate of the mortality associated with hypertensive disorders of pregnancy. When these data were sufficiently detailed, the proportion of deaths associated with eclampsia was also estimated.

Data were used as reported. No attempt was made to adjust for either coverage of births or deaths in hospital based studies, as in most cases the information on which such an adjustment should be based was not available.

Clearly these estimates are very crude, and to emphasize this they have been rounded to the nearest 5 per 100 000 live/total births. For the same reason confidence intervals have not been calculated. The denominator is described as live/total births. This is because studies vary in whether the denominator includes stillbirths, and some do not make this clear. In practice, the differences are small, and it seemed reasonable to ignore them.

## Results

For many countries there were no community-based data on maternal mortality. In Africa, estimates of maternal mortality derived from community-based studies were mostly based on small numbers of deaths (Table 1). In Asia, some community-based studies have recorded larger numbers of deaths (Table 2). There have been few community-based studies in Latin America and the Caribbean, and again the numbers of deaths recorded were relatively small (Table 3). Estimates of total maternal mortality were highest in Africa (Table 4), and generally lower in Latin America and the Caribbean (Table 5). The greatest range was in Asia (Table 6), where some countries had levels of mortality which were similar to those in Africa, while in a few Asian countries levels were comparable to those of Europe and North America.

Estimates of mortality associated with hypertensive disorders of pregnancy were similar in Africa, Latin America and the Caribbean, despite considerably higher total mortality in Africa. In Asia, as with overall mortality, the levels showed wide variation.

Within Africa, maternal mortality was lowest in the south, where the proportion of deaths due to hypertensive disorders of pregnancy was relatively high (10–27%), and mortality for hypertensive disorders of pregnancy was between 10–30 deaths per 100 000 live/total births. Estimates of total mor-

**Table 1.** Maternal mortality data in Africa

| Country | Years | Community-based studies | Other sources | Births | Maternal deaths |
|---|---|---|---|---|---|
| Algeria | 1963–84 | – | 4 | 596 819 | 854 |
| Botswana | 1982 | – | 1 | 24 457 | 22 |
| Burkina Faso | 1986 | – | 1 | 90 853 | 732 |
| Egypt | 1981–86 | 3 | – | 331 197 | 614 |
|  | 1973–86 | – | 7 | 84 652 | 661 |
| Ethiopia | 1981–83 | 1 | – | 9154 | 45 |
|  | 1980–85 | – | 4 | 120 722 | 793 |
| Gambia | 1951–87 | 4 | – | 7098 | 81 |
| Ghana | 1963–83 | – | 4 | 86 679 | 581 |
| Guinea | 1980–86 | – | 1 | 25 472 | 212 |
| Guinea-Bissau | 1977–87 | – | 6 | 34 125 | 278 |
| Ivory Coast | 1978–85 | – | 2 | 17 996 | 204 |
| Kenya | 1975–87 | 3 | – | 11 817 | 40 |
|  | 1972–81 | – | 2 | 25 803 | 102 |
| Liberia | 1974 | – | 1 | 13 858 | 24 |
| Libya | 1981–84 | – | 1 | 61 161 | 13 |
| Malawi | 1977 | 1 | – | 114 103 | 118 |
|  | 1976–89 | – | 5 | 107 116 | 459 |
| Mali | 1979–82 | – | 2 | 32 750 | 51 |
| Morocco | 1975–81 | – | 2 | 49 497 | 216 |
| Mozambique | 1984 | – | 1 | 10 769 | 40 |
| Niger | 1973–88 | – | 2 | 185 181 | 746 |
| Nigeria | 1961–69 | 1 | – | 2324 | 4 |
|  | 1958–88 | – | 22 | 687 579 | 4382 |
| Rwanda | 1966–71 | – | 3 | 193 311 | 1434 |
| Senegal | 1980–89 | 2 | – | 4776 | 33 |
|  | 1971–89 | – | 4 | 97 272 | 782 |
| Sierra Leone | 1969–81 | – | 3 | 89 032 | 567 |
| South Africa | 1972–82 | 1 | – | 364 | 2 |
|  | 1953–85 | – | 5 | 1 768 219 | 2030 |
| Sudan | 1962–84 | – | 7 | 141 399 | 717 |
| Swaziland | 1986–87 | – | 1 | 22 577 | 21 |
| Tanzania | 1983–85 | 2 | – | 147 701 | 119 |
|  | 1970–84 | – | 12 | 727 367 | 2242 |
| Togo | 1974 | – | 1 | 8608 | 41 |
| Tunisia | 1963–78 | – | 5 | 145 363 | 198 |
| Uganda | 1966–86 | – | 4 | 825 431 | 2836 |
| Zambia | 1974–88 | – | 4 | 315 664 | 458 |
| Zimbabwe | 1976–84 | – | 3 | 134 755 | 190 |

**Table 2.** Maternal mortality data in Asia

| Country | Years | Community-based studies | Other sources | Births | Maternal deaths |
|---|---|---|---|---|---|
| Afghanistan | 1973–74 | 1 | – | 1328 | 13 |
| | 1980–81 | – | 1 | 16 723 | 31 |
| Bahrain | 1977–86 | – | 1 | 109 221 | 37 |
| Bangladesh | 1967–85 | 4 | – | 120 354 | 682 |
| Bhutan | 1976–89 | – | 2 | 6243 | 55 |
| China | 1959–89 | 3 | – | 18 516 320 | 8278 |
| | 1962–71 | – | 2 | 46 000 | 5 |
| Hong Kong | 1945–83 | – | 2 | 2 428 331 | 556 |
| India | 1974–85 | 4 | – | 107 410 | 853 |
| | 1962–85 | – | 12 | 1 287 926 | 8341 |
| Indonesia | 1980–87 | 2 | – | 53 418 | 345 |
| | 1969–82 | – | 3 | 48 351 | 282 |
| Iran | 1970–76 | – | 2 | 54 381 | 125 |
| Israel | 1954–76 | – | 1 | 63 997 | 27 |
| Japan | 1982–86 | – | 1 | 7 328 382 | 1154 |
| Jordan | 1979 | – | 1 | 31 018 | 15 |
| Kuwait | 1969–80 | – | 1 | 495 059 | 93 |
| Laos | 1986–87 | – | 1 | 14 103 | 51 |
| Lebanon | 1971–82 | – | 1 | 35 058 | 45 |
| Malaysia | 1976–73 | 2 | – | 96 317 | 65 |
| | 1967–73 | – | 2 | 282 774 | 696 |
| Myanmar | 1973–87 | – | 3 | 119 525 | 358 |
| Nepal | 1975–81 | 3 | – | 2470 | 28 |
| | 1979–85 | – | 2 | 45 175 | 88 |
| Pakistan | 1977–87 | 1 | – | 2145 | 4 |
| | 1975–86 | – | 9 | 120 106 | 1117 |
| Philippines | 1972 | 1 | – | 49 314 | 35 |
| | 1974–86 | – | 2 | 2 430 974 | 3749 |
| Qatar | 1977–85 | – | 1 | 63 492 | 9 |
| Saudi Arabia | 1978–80 | – | 2 | 56 428 | 30 |
| Singapore | 1978–88 | – | 1 | 40 155 | 14 |
| Syria | 1963–81 | – | 3 | 24 942 | 85 |
| Thailand | 1977–83 | 1 | – | 3951 | 9 |
| | 1968–83 | – | 4 | 602 095 | 401 |
| Turkey | 1975–86 | 2 | – | 35 767 | 46 |
| | 1971–81 | – | 1 | 20 291 | 13 |
| Viet Nam | 1984–85 | – | 1 | 22 190 | 128 |
| Yemen | 1977–86 | – | 1 | 41 564 | 291 |

tality were highest in West Africa as were estimates of mortality associated with hypertensive disorders of pregnancy (35–150 deaths per 100 000 births). With one exception, the proportion of maternal deaths in West Africa due to hypertensive disorders of pregnancy ranged from 7 to 18%.

**Table 3.** Maternal mortality in Latin America and the Caribbean

| Country | Years | Community-based studies | Other sources | Births | Maternal deaths |
|---|---|---|---|---|---|
| Argentina | 1987 | 1 | – | 22 756 | 41 |
| Brazil | 1986 | 1 | – | 224 850 | 218 |
| | 1970–87 | – | 4 | 92 267 | 131 |
| Chile | 1961–79 | – | 2 | 558 536 | 607 |
| Colombia | 1965–73 | – | 3 | 146 807 | 435 |
| Ecuador | 1980–85 | – | 3 | 1 510 851 | 2457 |
| Guyana | 1971 | – | 1 | 23 787 | 42 |
| Honduras | 1974 | – | 1 | 126 166 | 160 |
| Jamaica | 1981–83 | 2 | – | 230 150 | 243 |
| | 1977–79 | – | 2 | 190 279 | 93 |
| Mexico | 1969–73 | – | 1 | 38 972 | 140 |
| Paraguay | 1977 | 1 | – | 31 850 | 149 |
| Peru | 1962–85 | – | 2 | 112 614 | 184 |
| Puerto Rico | 1978–79 | 1 | – | 148 901 | 62 |
| Trinidad and Tobago | 1981–86 | – | 1 | 34 727 | 11 |
| Venezuela | 1961–75 | – | 3 | 579 824 | 730 |

It is impossible to make any generalizations about maternal mortality in Asia. Total mortality in Eastern Asia was in a similar range to Europe and North America. Mortality due to hypertensive disorders of pregnancy was also low (5 deaths per 100 000 births), although between 10 and 30% of deaths were attributable to hypertensive disorders of pregnancy. In contrast, total maternal mortality in South Asia was high, with some countries having levels which were similar to the worst found in Africa. Hypertensive disorders of pregnancy were associated with between 9 and 15% of deaths in this region, and mortality for hypertensive disorders of pregnancy was also high (25–120 deaths per 100 000 births).

Most countries in South East Asia had moderate to high maternal mortality, and for hypertensive disorders of pregnancy, mortality was between 25 and 65 deaths per 100 000 live/total births. The exceptions were Singapore and Thailand, where both total maternal mortality and mortality associated

**Table 4.** Estimates of cause-specific mortality for hypertensive disorders of pregnancy (HDP) (per 100 000 live/total births) in Africa

| Country | Estimated maternal mortality | Percentage of deaths due to HDP | Estimated mortality for HDP |
|---|---|---|---|
| East Africa | | | |
| Ethiopia | 645 | 8 | 50 |
| Kenya | 215 | 3 | 10 |
| Malawi | 260 | 4 | 10 |
| Mauritius‡ | 95 | 12 | 10 |
| Mozambique | 370 | 23 | 85 |
| Tanzania | 270 | 7 | 20 |
| Uganda | 345 | 3 | 10 |
| Zambia | 145 | 21 | 30 |
| Zimbabwe | 140 | 9 | 15 |
| North Africa | | | |
| Algeria | 140 | 9 | 15 |
| Egypt | 305 | 15 | 45 |
| Morocco | 435 | 7 | 30 |
| Sudan | 515 | 13 | 70 |
| Tunisia | 135 | 12 | 15 |
| West Africa | | | |
| Burkina Faso* | 810 | 1 | 10 |
| Ghana | 670 | 9 | 60 |
| Guinea* | 835 | 15 | 125 |
| Guinea-Bissau | 790 | 17† | 135 |
| Ivory Coast | 1140 | 8 | 90 |
| Niger | 390 | 18 | 70 |
| Nigeria | 590 | 12 | 70 |
| Senegal | 795 | 11† | 90 |
| Sierra Leone | 635 | 12 | 75 |
| The Gambia | 1130 | 13 | 150 |
| Togo | 475 | 7 | 35 |
| Central Africa | | | |
| Cameroon | 145 | 4 | 10 |
| Chad* | 835 | 21 | 175 |
| Congo | 80 | 10 | 10 |
| Gabon | 155 | 10 | 15 |
| Zaire | 105 | 10 | 10 |
| Southern Africa | | | |
| Botswanna* | 90 | 27 | 25 |
| South Africa | 115 | 26 | 30 |
| Swaziland | 95 | 10 | 10 |

*Data from one hospital only.
†Cause of death data on less than 20% of recorded deaths
‡Vital registration data only.

**Table 5.** Estimates of cause-specific mortality for hypertensive disorders of pregnancy (HDP) (per 100 000 live/total births) in Latin America

| Country | Estimated maternal mortality | Percentage of deaths due to HDP | Estimated mortality for HDP |
|---|---|---|---|
| Central America | | | |
| Mexico* | 360 | 37 | 135 |
| Caribbean | | | |
| Jamaica | 80 | 30 | 25 |
| Puerto Rico | 40 | 35 | 15 |
| Trinidad and Tobago*† | 30 | 73 | 20 |
| Tropical South America | | | |
| Brazil | 110 | 17 | 20 |
| Colombia | 295 | 21 | 60 |
| Ecuador | 165 | 25 | 40 |
| Paraguay† | 470 | 13 | 60 |
| Peru | 165 | 17 | 30 |
| Venezuela | 125 | 23 | 30 |
| Temperate South America | | | |
| Argentina | 180 | 10 | 20 |
| Chile | 110 | 10 | 10 |

*Data from one hospital only.
†Vital registration data only

with hypertensive disorders of pregnancy were lower. In South West Asia, both maternal mortality and mortality associated with hypertensive disorders of pregnancy varied from very low to very high levels.

Estimates of maternal mortality were relatively low in the Caribbean. In this region the proportions of deaths associated with hypertensive disorders of pregnancy was extremely high (30–73%), and mortality for hypertensive disorders of pregnancy was between 15 and 25 deaths per 100 000 live/total births . In temperate South America, total mortality was a little higher and the proportion of deaths due to hypertensive disorders of pregnancy was lower at 10%. Here mortality for hypertensive disorders of pregnancy was 10–20 deaths per 100 000 live/total births.

Maternal mortality was higher in tropical South America, where between 13 and 25% of deaths were associated with hypertensive disorders of pregnancy. Mortality associated with hypertensive disorders of pregnancy was 20–60 deaths per 100 000 live/total births. For Central America, data were only available from a single hospital in Mexico.

These estimates have many limitations, which are discussed more fully below, but they suggest that between 10 and 15% of all maternal deaths are associated with hypertensive disorders of pregnancy. In addition, for the small number of countries where more detailed data were available on cause of death, estimates of the proportion of deaths associated with hypertensive disorders of pregnancy which were also associated with eclampsia were mostly between 60% and 100% (Tables 7–9). Where the mortality associated with hypertensive disorders of pregnancy was highest, the proportion of deaths associated with eclampsia also tended to be high. This suggests that around 10% of all maternal deaths (50 000 per year world wide) are associated with eclampsia.

## Discussion

Most of the data reviewed for the study were hospital-based. The limitations and potential biases of such data are widely recognized, particularly when no adjustment is made for expected place of delivery or coverage of births (Chalmers & Macfarlane 1980; Royston & AbouZahr 1992). A few studies were community-based (Koenig *et al.* 1988; Kwast *et al.* 1986; Boerma & Mati 1989). These studies are often conducted in relatively small areas and are rarely repeated because they are time consuming and expensive, in terms of both financial and other resources. Although they provide more accurate data for the area in which they were conducted, they are not necessarily generalizable to the rest of the country, and the small numbers of deaths upon which they are based mean that they usually yield very imprecise estimates of the frequency of maternal mortality.

Most of the Latin American and Caribbean data were derived from birth and death registrations. The recording of such vital events is more complete than in Africa and Asia, but, as far back as 1967, data on cause of death had been shown to be very inadequate (Puffer & Griffith 1967). This is particularly important for maternal deaths. Deaths will only be recorded as 'maternal' if pregnancy is mentioned on the death certificate. A small number of more recent studies in several

**Table 6.** Estimates of cause-specific mortality for hypertensive disorders of pregnancy (HDP) (per 100 000 live/total births) in Asia

| Country | Estimated maternal mortality | Percentage of deaths due to HDP | Estimated mortality for HDP |
|---|---|---|---|
| South East Asia | | | |
| Myanmar | 300 | 11† | 35 |
| Indonesia | 470 | 14 | 65 |
| Malaysia | 270 | 16 | 45 |
| Philippines | 150 | 22 | 35 |
| Singapore | 35 | 21 | 10 |
| Thailand | 90 | 11 | 10 |
| Viet Nam | 575 | 4 | 25 |
| Eastern Asia | | | |
| China | 45 | 10 | 5 |
| Hong Kong | 25 | 22 | 5 |
| Japan‡ | 15 | 30 | 5 |
| South West Asia | | | |
| Bahrain‡ | 35 | 15 | 5 |
| Israel* | 40 | 15 | 10 |
| Kuwait | 20 | 22 | 5 |
| Lebanon* | 130 | 7 | 10 |
| Qatar* | 15 | 55 | 10 |
| Saudi Arabia | 55 | 3 | 5 |
| Syria | 340 | 11 | 40 |
| Turkey | 105 | 11 | 10 |
| Yemen | 700 | 13 | 90 |
| Middle South Asia | | | |
| Bangladesh | 565 | 15 | 85 |
| Bhutan | 875 | 9 | 80 |
| India | 640 | 11 | 70 |
| Nepal | 245 | 9 | 25 |
| Pakistan | 905 | 13 | 120 |

*Data from one hospital only.
†Cause of death data on less than 20% of recorded deaths.
‡Vital registration data only.

**Table 7.** Estimates of the percentage of maternal deaths associated with hypertensive disorders of pregnancy (HDP) which are also associated with eclampsia in Africa

| Country | Maternal deaths | Deaths associated with HDP | Deaths associated with eclampsia | Percentage of HDP deaths associated with eclampsia |
|---|---|---|---|---|
| Egypt | 69 | 15 | 8 | 53 |
| Nigeria | 116 | 18 | 16 | 89 |
| Tanzania | 224 | 43 | 25 | 58 |

countries have validated cause of death as recorded at death certification. They have found between 54 and 72% under-ascertainment of maternal deaths (Molina Morey de Illia unpublished document 1989; Laurenti 1988; Speckhard 1985; Walker *et al.* 1985). Even in countries with far better developed systems of vital event registration, there is considerable under-ascertainment of maternal deaths. For example, in the United States routine death certificate surveillance in Georgia during 1975–76 understated the true number of maternal deaths by between 27 and 50% (Rubin *et al.* 1981). In addition, comparisons between national and state surveillance suggested that national statistics in the United States underestimate the number of maternal deaths by 20% (Smith *et al.* 1984).

Maternal deaths are relatively rare events, even in areas where maternal mortality is very high. This contributes to the difficulties of measuring maternal mortality. It also means that estimates of maternal mortality are likely to be based on small numbers of deaths, and to have large standard errors. Random variation may therefore explain some of the differences in levels reported for one particular area, or from similar areas. For example, in Jamaica there are four sources of maternal mortality data. Two of these were community-based studies, one was hospital-based, and the fourth was based on vital registration data (Table 10). The reported estimates of maternal mortality range from 48 to 115 deaths per 100 000 live births. However, the 95% confidence intervals were all wide and have considerable overlap, so the estimates are not, in fact, all incompatible.

**Table 8.** Estimates of the percentage of maternal deaths associated with hypertensive disorders of pregnancy (HPD) which are also associated with eclampsia in Asia

| Country | Maternal deaths | Deaths associated with HDP | Deaths associated with eclampsia | Percentage of HDP deaths associated with eclampsia |
|---|---|---|---|---|
| Bahrain | 37 | 5 | 4 | 80 |
| Bhutan | 44 | 4 | 3 | 75 |
| India | 7985 | 730 | 653 | 89 |
| Indonesia | 50 | 8 | 8 | 100 |
| Iran | 125 | 9 | 9 | 100 |
| Israel | 27 | 4 | 3 | 75 |
| Japan | 406 | 125 | 50 | 40 |
| Kuwait | 50 | 11 | 9 | 82 |
| Lebanon | 45 | 3 | 3 | 100 |
| Malaysia | 726 | 125 | 70 | 58 |
| Myanmar | 44 | 5 | 5 | 100 |
| Nepal | 81 | 6 | 6 | 100 |
| Pakistan | 545 | 72 | 69 | 96 |
| Qatar | 9 | 5 | 4 | 80 |
| Syria | 22 | 2 | 2 | 100 |
| Thailand | 263 | 35 | 23 | 66 |
| Yemen | 482 | 30 | 29 | 97 |

Despite their limitations, these data reflect the experiences of the women who gain access to the health services. They suggest that between 10 and 15% of maternal deaths which these women experience are associated with hypertensive disorders of pregnancy, and that around 10% of all maternal deaths of women who reach hospital are associated with eclampsia. It should be possible to prevent many of these deaths.

Although a woman's risk of dying from a given pregnancy is higher in Africa than in Latin America and the Caribbean (Royston & Armstrong 1989; Boerma 1987), the estimates of mortality presented in this paper suggest the risk of dying from hypertensive disorders of pregnancy may well be similar in these two continents. Furthermore, there is no evidence that this risk is decreasing, either in Africa, or in Latin America. Indeed, data from one city in Brazil suggest that it may even be increasing in some places (Laguardia *et al.* 1990). These observations imply that it is largely reductions in mortality associated with infection and haemorrhage which have led to the decline in maternal mortality overall in Latin America and the Caribbean. They also support other evidence suggesting that deaths associated with hypertensive disorders of pregnancy are the most difficult to prevent in developing, as well as developed, countries (Moodley 1990; Loudon 1991). Hypertensive disorders of pregnancy are thus likely to become a problem of increasing importance in the future, as deaths from other causes are reduced, particularly in the developing world.

In some areas of Asia, such as Japan, Singapore and Hong Kong, levels of overall maternal mortality and of mortality due to hypertensive disorders of pregnancy seem to be similar to those in Europe and North America. Estimates based on the sources that were available for this study suggested that maternal mortality was also low in China, although more recent data have suggested that the true level may be higher (100 deaths per 100 000 live/total births) (unpublished report). China is an outstanding example of a country which although still largely underdeveloped, has reasonable coverage of low technology health care. For other countries, particularly those in South Asia, such as Bhutan, Pakistan and India, the situation is very different and estimates of overall maternal mortality and of mortality associated with hypertensive disorders of pregnancy were very high.

The available evidence also suggests that, despite being a rare complication of pregnancy, eclampsia is an important cause of maternal death, even in developed countries (Redman 1988). For example, in England and Wales between 1970 and 1987, 56% of deaths associated with hypertensive disorders of pregnancy were attributable to eclampsia (Department of Health 1991). Evidence presented in this paper suggests that eclampsia is also an important cause of maternal death in many parts of Africa, Asia, Latin America, and the Caribbean.

**Table 9.** Estimates of the percentage of maternal deaths associated with hypertensive disorders of pregnancy (HDP) which are also associated with eclampsia in Latin America

| Country | Maternal deaths | Deaths associated with HDP | Deaths associated with eclampsia | Percentage of HDP deaths associated with eclampsia |
|---|---|---|---|---|
| Brazil | 34 | 8 | 8 | 100 |
| Chile | 454 | 49 | 36 | 74 |
| Jamaica | 181 | 49 | 37 | 76 |

**Table 10.** Maternal mortality studies in Jamaica

| Maternal mortality* | (95% CI) | Maternal deaths | Years | Type of study |
|---|---|---|---|---|
| 103 | 88–118 | 181 | 1981–83 | Community-based |
| 115 | 86–144 | 62 | 1986–87 | Community-based |
| 60 | 18–101 | 8 | 1982 | Hospital-based |
| 48 | 38– 58 | 85 | 1977–79 | Vital event registration |

*per 100 000 live births.

An analysis of the decline in maternal mortality in Sweden suggests that when the mortality associated with eclampsia is very high, the initial decline is likely to come from a fall in the case fatality rate, rather than from changes in the incidence (Hogberg & Joelsson 1985). There is, however, considerable disagreement about the most effective management of eclampsia, and much of the discussion has focused on which is the optimal anticonvulsant. Uncontrolled evidence may suggest very large treatment differences, but more moderate effects can only be estimated reliably in sufficiently large randomized trials. A difference of 20% in the risk of maternal death between two treatments for eclampsia would be regarded by most people as substantial. Yet this difference is impossible to detect either by clinical experience alone, or by small trials in single centres. What is required are large, multicentre studies. One such trial is currently recruiting in South America, and will soon be extended to centres in Africa and Asia (Duley 1992). The main comparison in this trial is between care based on magnesium sulphate, and care based on diazepam, but one centre is comparing phenytoin with magnesium sulphate. The aim is to estimate reliably the differential effects of these treatments on maternal mortality and serious morbidity, and on perinatal mortality and morbidity.

A recent overview (meta analysis) of randomized controlled trials of antiplatelet agents in the prevention of pre-eclampsia provides evidence that these drugs reduce the incidence of proteinuric pre-eclampsia (Collins 1992). It is plausible that this reduction in incidence could also lead to a reduction in the mortality associated with both pre-eclampsia and eclampsia. The trials conducted so far, however, have been too small to allow reliable evaluation of the effects on maternal and perinatal mortality, or on other rare but serious outcomes. A large multicentre study is currently recruiting in 17 countries (Farrell & Grant 1992), and between 9 and 10 000 women will have been entered by the end of 1992, when recruitment ceases. The results of this study will provide more reliable assessments of both the effectiveness and the safety of antiplatelet agents. These studies have been largely conducted in developed countries, but they have important implications for maternal health in developing countries, where the potential for benefits is high but the risk of adverse effects may also be increased. A large multicentre trial is currently being conducted in Brazil (Atallah 1992). This trial is the first to assess the effects of antiplatelet agents in a developing country. Other, similar trials are planned in Barbados (Rotchell 1992) and Jamaica (Ashley 1992). The results of these studies will be of great importance, as it is developing countries which bear the greatest burden of mortality, and morbidity, from hypertensive disorders of pregnancy.

In summary, there is considerable variation in maternal mortality throughout the world, and almost all these deaths are of women who would survive in the developed world. Where overall mortality is highest, deaths from haemorrhage and infection account for a large part of the excess. Hypertensive disorders of pregnancy are an important cause of maternal mortality throughout the world, and the majority of these deaths are associated with eclampsia. There is considerable disagreement about what is the optimal management of women with eclampsia. How to reduce deaths associated with hypertensive disorders of pregnancy will not become clear until there is better evidence than is currently available.

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OBSTETRICS

# Management of severe pre-eclampsia and eclampsia by UK consultants

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## ABSTRACT

**Objective** To determine the current management of severe pre-eclampsia and eclampsia in the United Kingdom.

**Design** One-page postal survey to all (1007) UK consultant obstetricians with questions about use of antihypertensive and anticonvulsant drugs in severe pre-eclampsia and eclampsia, other management strategies, definition of factors determining severity, protocol development and regional review.

**Results** 688 replies (69·6% response rate). The antihypertensive drugs used were mainly oral labetalol (35%), oral methyl dopa (23%) and parenteral hydralazine (29%); diuretics were not used. Diazepam was the preferred drug in eclampsia. Very few consultants used magnesium sulphate (2%). Anticonvulsants were also prescribed by 85% of consultants to prevent fits; the drugs then preferred were diazepam (41%), phenytoin (30%) and chlormethiazole (24%). Two-thirds of consultants felt there was a need for trials to study the effectiveness of antihypertensive and anticonvulsant drugs. In a woman with proteinuric hypertension, 15% of consultants did not regard the development of headache as indicating severe pre-eclampsia. Consistent management practices were not associated with agreement about protocols. Regional review does not appear to have occurred.

**Conclusion** Antihypertensive and anticonvulsant therapies are widely used but trials are considered necessary. Improvements in the management of women with severe pre-eclampsia or eclampsia might occur if UK obstetricians sought more collective opinion and undertook regional audit of protocols.

Hypertensive disorders of pregnancy rank with pulmonary embolism as the commonest cause of maternal death in the United Kingdom. The two latest maternal mortality reports (Department of Health 1989 and 1991) have cited potentially avoidable factors in the management of severe pre-clampsia and eclampsia. Examples of suboptimal care have been failures to control hypertension, to administer anticonvulsants prophylactically, or to deliver the woman expeditiously. Recommendations have also been made about standardized hospital protocols and regional reviews of management.

The management of hypertension in pregnancy was last determined by Chamberlain *et al.* (1978) in a questionnaire sent to all members and fellows of the Royal College of Obstetricians and Gynaecologists (RCOG) in the UK and Eire in 1976.

The objective of this study was to determine the management of women with severe pre-eclampsia and eclampsia by consultants throughout the UK in 1991 and to compare these practices with those reported previously (Chamberlain *et al.* 1978). A secondary objective was to determine if these consultants felt any comparative studies on the effectiveness of antihypertensive and anticonvulsant drug treatments were needed.

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## Method

A questionnaire requiring 39 responses was designed. After piloting and minor modification, the questionnaire was mailed in March 1991 to 1007 consultant obstetricians whom the Royal College of Obstetricians and Gynaecologists (RCOG) had listed as employed in a maternity hospital in the UK in May 1990. After 8 weeks, a further questionnaire was mailed to non-responders.

After 4 months, all the responses were analysed. When consultants were listed at two hospitals, they were allocated to the larger hospital. The number of deliveries per annum, and the number of neonatal intensive care cots at each hospital were taken from the Directory of Emergency and Special Care Units (1991). The statistical analyses used the $\chi^2$-test.

The present report represents a synthesis of the results and our conclusions. Detailed results can be obtained on request.

## Results

### *1. Study population*

There were 688 replies for analysis from obstetricians in active practice (response rate = 69·6%). Of the 271 hospitals that employed obstetric consultants, replies were received from 259 (95·6%). There were no hospital or regional biases in the number of consultants replying, nor in the time since they had obtained their MRCOG.

### *2. Management strategies*

### *Use of antihypertensive therapy*

The number of consultants prescribing different antihypertensive therapy for antenatal pre-eclampsia, and the diastolic blood pressure (DBP) at which the therapy would be initiated are shown in Table 1.

The DBP at which antihypertensive therapy would be initiated ranged, with one exception, between 90 and 125 mmHg. Oral antihypertensive therapy was usually initiated at DBP levels <110 mmHg, whereas parenteral therapy was preferred above this value ($\chi^2$=114·45; $P$<0·001).

After an eclamptic fit, almost all consultants prescribed an antihypertensive if there was hypertension. Most consultants then administered the therapy parenterally, and then usually as hydralazine ($n$=513; 86%). More than 40% ($n$=126) of the consultants who used parenteral labetalol in treating antenatal pre-eclampsia, used hydralazine in eclampsia whereas only 3% ($n$=6) of those who used antenatal hydralazine changed this antihypertensive in the post-eclamptic setting.

### *Use of anticonvulsant therapy*

Most consultants ($n$=566; 84%) advised an anticonvulsant to prevent (as opposed to treat) fits in women with severe pre-eclampsia. The choices of drugs and the routes of administration are shown in Table 2. Diazepam was the most commonly used drug.

**Table 1.** Number of consultants prescribing different antihypertensive therapy for antental pre-eclampsia, and the diastolic blood pressure at which the therapy would be initiated*

| Antihypertensive | Diastolic blood pressure (mmHg) | | | | |
|---|---|---|---|---|---|
| | *n* 90-99 | *n* 100-109 | *n* 110-119 | 120+ | Total *n* (%) |
| Oral | | | | | |
| Labetalol | 30 | 141 | 37 | 1 | 209 (35·0) |
| Atenolol | 4 | 16 | 6 | 0 | 26 (4·4) |
| Methyl dopa | 21 | 81 | 31 | 1 | 134 (22·6) |
| Hydralazine | 0 | 4 | 1 | 0 | 5 (0·8) |
| Nifedipine | 1 | 9 | 12 | 0 | 22 (3·7) |
| Parenteral | | | | | |
| Labetalol | 0 | 17 | 9 | 1 | 27 (4·5) |
| Atenolol | 0 | 2 | 1 | 0 | 3 (0·5) |
| Hydralazine | 2 | 44 | 115 | 9 | 170 (28·5) |
| Total *n* (%) | 58 (9·8) | 314 (52·5) | 212(35·5) | 12 (2·0) | 596 |

* Excludes one consultant who prescribed methyldopa at a diastolic blood pressure of 85 mmHg.

Diazepam was the drug chosen to treat a woman during and 10 min after an eclamptic fit by 82% of the consultants. However, over half the consultants changed drugs in the post-seizure setting, choosing drugs which closely correlated with their choice of prophylactic anticonvulsant (Table 2).

### *3. Support for a trial to compare drug therapies*

A trial comparing antihypertensive drugs used in the management of severe pre-eclampsia was supported by 392 (65%) of consultants.

A number of consultants ($n$=388; 64%) felt there was a need for a trial comparing anticonvulsant drugs to prevent fits in severe pre-eclampsia. Twenty consultants suggested such a trial should have a group allocated to a placebo.

### *4 Assessment of severity of pre-eclampsia*

How consultants judge the severity of pre-eclampsia was determined from the responses to a hypothetical case example. Most consultants regarded the development of vomiting or epigastric pain as indicating 'very severe' or 'severe' pre-eclampsia, but 99 consultants (15%) did not give this degree of significance to a report of headache.

### *5. Hospital protocols and regional review*

Most consultants ($n$=590; 87%) from 157 hospitals stated there was a written protocol for the management of severe pre-eclampsia in their hospital. However, when the consistency of use by consultants of particular managements within each of these 157 hospitals where there was agreement about protocol was compared, there were no significant correlations.

Nearly 60% of consultants ($n$=401; 58%) indicated there had been a review of the management of severe pre-eclampsia in their region in the last 5 years. These positive responders were evenly distributed between the regions. The remaining 287 consultants (42%) were of the opinion that there had been no regional review!

## Discussion

The response rate for practising obstetricians of 70% in this survey is more than the 56% obtained in the previous survey by Chamberlain *et al.* (1978).

**Table 2.** Number of consultants prescribing various anticonvulsants to prevent fits in severe pre-eclampsia, and the route of administration of this anticonvulsant

| Prophylactic anticonvulsant | Route of administration | | | Responses *n* (%) |
|---|---|---|---|---|
| | iv | im or sc | oral | |
| Diazepam | 204 | 12 | 9 | 226 (40·8) |
| Clormethiazole | 120 | 0 | 1 | 130 (23·6) |
| Phenytoin | 106 | 12 | 49 | 167 (30·3) |
| Magnesium sulphate | 8 | 3 | 0 | 11 (2·0) |
| Other (incl barbiturate) | 4 | 7 | 7 | 20 (3·3) |
| Total *n* (%) | 452 (81·8) | 35 (6·2) | 67 (12·0) | 554 |

Abbreviations: iv=intravenous; im=intramuscular; sc=subcutaneous.

This survey, unlike that by Chamberlain *et al* (1978), did not include obstetricians in Eire, or members of the RCOG who were registrars or senior registrars. However, this survey of consultant obstetricians provides a national picture of the current management of women with severe pre-eclampsia and eclampsia by those who are ultimately responsible for the management. The actual management would, of course, be better ascertained by a prospective audit such as that planned for eclampsia in 1992 by the British Eclampsia Survey Team (BEST) (Douglas & Redman 1992).

Antihypertensive drug therapy is now routine practice in the management of women with severe pre-eclampsia and eclampsia whereas 15 years ago it was used by only 55% of obstetricians (Chamberlain *et al.* 1978). Oral therapy is now started at a diastolic blood pressure of ≥100 mmHg by 34% of consultants compared with 9% of consultants in the previous study. Labetalol is now the favourite oral antihypertensive drug, whereas it was not mentioned in 1978. However, hydralazine is still the most preferred antihypertensive drug in the management of eclampsia.

The most marked change in antihypertensive therapy in the UK in recent years has been that diuretic drugs are no longer used. In 1978, frusemide was prescribed 'frequently' by 41% of obstetricians whereas it was not routinely used in the present survey. Other antihypertensive drugs such as veratrum, clonidine and diazoxide, which were frequently used by many practitioners in the 1978 report are now obsolete.

Another new antihypertensive agent, nifedipine, is used by 3·7% of consultants for antenatal hypertension, and by 1·7% in eclampsia. In New Zealand, where the national use of antihypertensive drugs has also been studied recently (Hutton *et al.* 1990), 11% of consultants prescribed nifedipine in fulminating pre-eclampsia; otherwise, the pattern of use of antihypertensive drugs in New Zealand was similar to the findings in this UK study.

Anticonvulsant therapy has also undergone a marked change in recent years. In the 1978 survey, the most commonly used anticonvulsants were diazepam (61%), chlormethiazole (26%) and barbiturates (18%); phenytoin was not mentioned. In 1991, diazepam still remains popular (41%) but phenytoin is now used more commonly than chlomethiazole with 30% of UK consultants prescribing phenytoin in imminent eclampsia. Barbiturates and tribromethanol are now rarely, if ever, used.

Since the last survey, there has been almost no change in use of magnesium sulphate. It is prescribed by few consultants (1·8%) which compares with 11% by fellows of the Australian RCOG (Trudinger & Parik, 1982) and 8% by New Zealand obstetricians (Hutton *et al.* 1990). In the US, magnesium sulphate is very widely used (Lewis *et al.* 1980; Sibai 1990) and is 'the drug of choice to prevent or treat eclamptic convulsions' (Consensus Report 1990).

The onset of headache was considered by our respondents to be of less importance than any other development. This disturbing practice of trivializing the symptom of headache in women with proteinuric hypertension was also highlighted in the 1982-84 maternal mortality report (DoH 1989). In contrast, nearly all consultants regarded the development of epigastric pain in an inpatient with hypertension and proteinuria as indicating at least severe pre-eclampsia.

The inconclusive results to the question about regional review in this survey do suggest that those reviews that have been undertaken have lacked leadership and/or adequate communication with colleagues. Consultants also appear confused about the existence of management protocols in their hospitals. In this study, the only significant association of an agreed protocol with a consistent management practice in a hospital was weak. Closer agreement about the use of protocols that detail specific anticonvulsant and antihypertensive therapy as well as other specific managements will need to occur if the current high rate (>50%) of fatal eclamptic fits that occur under medical supervision is to fall. The significant differences in drug regimens and delivery practices between consultants in teaching hospitals and those in smaller hospitals noted in this study also highlight deficiences in communication between consultants and a lack of regional strategies, both of which probably need to be addressed if the mortality associated with severe pre-eclampsia and eclampsia is to improve.

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# Management of prelabour rupture of the membranes in term primigravidae: report of a randomized prospective trial

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**ABSTRACT**

**Objective** To compare a conservative and an active policy (immediate oxytocin infusion) of management of prelabour rupture of the membranes in term primigravidae.

**Design** Randomized trial involving 444 women.

**Setting** District maternity hospital.

**Main outcome measures** Caesarean section rate in each group; also the rate of forceps deliveries, spontaneous deliveries, length of labour, number of vaginal examinations, type of analgesia, pyrexia in labour or the puerperium and antibiotic use in the mother and the infant in each group. The caesarean section rate for the whole trial where the latent period was >12 h was compared to that where the latent period was ≤12 h.

**Results** There were fewer caesarean sections in the conservative group (odds ratio (OR) 0·60, 95% confidence interval (CI) 0·35 to 1·02; *P* = 0·06). There was a similar number of forceps deliveries (OR 0·79; 95% CI 0·52 to 1·19; *P* = 0·26) but more spontaneous deliveries (OR 1·57; 95% CI 1·08 to 2·29; *P* = 0·02) in the conservative group. More women managed conservatively required inhalational analgesia only for pain relief in labour (OR 2·88; 95% CI 1·46 to 5·68; *P* = 0·003), a similar number required pethidine (OR 1·29; 95% CI 0·85 to 1·94; *P* = 0·23), and fewer required epidural analgesia (OR 0·57; 95% CI 0·39 to 0·84; *P* = 0·005). The number of vaginal exminations was less in the conservative group (difference between means 0·53; 95% CI 0·25 to 0·80; *P*<0·001). Fewer women managed conservatively experienced four or more vaginal examinations in labour (OR 0·58; 95% CI 0·39 to 0·86; *P* = 0·007). There were no differences in the lengths of labour, the proportions of women who developed pyrexia in labour or the puerperium or who required antibiotics or in the proportions of infants who required antibiotics.

**Conclusions** These results argue in favour of a conservative policy in managing primigravidae at term with prelabour rupture of the membranes.

Prelabour rupture of the membranes at term is common, occurring in 6 to 19% of all term births (Grant & Keirse 1989). Management is not clear, the main uncertainty relating to induction of labour or expectant care. Three decades ago the main worry of prelabour rupture of the membranes was intrauterine infection and this led to the widespread adoption of a policy of induction of delivery to prevent such infection. More recently this view has been challenged by an apparent increase in the number of caesarean sections in women with prelabour rupture of the membranes who had their labours induced (Kappy *et al.* 1979, 1982; Conway *et al.* 1984).

There have been five controlled comparisons of active and conservative policies (Table 1). In four of these trials the active management was an immediate oxytocin infusion; in all of these trials formal randomization was not used and therefore their results are in doubt. In the trial by Duff *et al.* (1984) women were allocated to different treatment policies according to the day of the week on which they were admitted to hospital. Since two obstetric teams were responsible for the labour suite on alternate days of the week any difference in caesarean section rates may have been as much due to different policies in managing labour as to an active compared with a conservative policy. Fayez *et al.* (1978) and Wagner *et al.* (1989) allocated the women under their care by case record number, while Morales & Lazar (1986) used both case record number and day of the week in their allocation of women to induction of labour or expectant care. In every case prior knowledge of the treatment allocation may have led to a selection bias, and so the results of the trials, apparently showing fewer caesarean sections in the conservative groups, must be in doubt. That such a selection bias is probable is suggested by the greater number of

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**Table 1.** Results of quasi-randomized trials of active compared to conservative management of prelabour rupture of the membranes at term on caesarean section rates

| Study | Active management | Conservative management | Odds ratio | (95% CI) |
|---|---|---|---|---|
| Fayez *et al.* (1978) | 3/53 (5·7%) | 2/59 (3·4%) | 1·69 | (0·28 to 10·13) |
| Duff *et al* (1984) | 12/59 (20·3%) | 5/75 (6·7%) | 3·40 | (1·23 to 9·45) |
| Morales & Lazar (1986) | 31/150 (20·7%) | 11/167 (6·6%) | 3·39 | (1·77 to 6·49) |
| Wagner *et al.* (1989) | 12/86 (14·0%) | 15/96 (15·6%) | 0·88 | (0·39 to 1·98) |
| Mahmood *et al.* (1989) | 5/48 (10·4%) | 6/52 (11·5%) | 0·89 | (0·26 to 3·11) |
| Typical odds ratio (95% CI) | | | 2·15 | (1·42 to 3·25) |

women allocated to expectant care in the four trials. In the fifth trial, where the active management was vaginal prostaglandin $E_2$ gel, the method of randomization was not specified (Mahmood *et al.* 1989). Table 1 is an overview of these trials.

It was owing to this uncertainty that we undertook our own trial to compare a conservative and an active policy in women admitted at term with prelabour rupture of the membranes, which we confined to primigravidae.

## Subjects and methods

Primigravidae admitted at term with prelabour rupture of the membranes were eligible for entry. Women who had a history suggestive of spontaneous rupture of the membranes and who did not have a history of uterine contractions were subjected to a sterile speculum examination in the labour ward by the senior house officer or registrar on duty; no other tests of spontaneous rupture of the membranes, such as the pH of the vagina or the presence of ferns on microscopy were made (Friedman & McElin, 1969; Smith, 1976; Gorodeski *et al.* 1982). Owing to fear of introducing intrauterine infection a digital vaginal examination to assess the cervix was not performed. After diagnosis of spontaneous rupture of the membranes cardiotocography using an external ultrasound transducer was performed and the uterus palpated by a midwife for an hour. If the fetal heart rate trace was normal and if contractions were not palpated the top one of a numbered series of opaque, sealed envelopes containing the randomization codes was opened.

### *Active policy*

Women randomized to the active policy received an intravenous oxytocin infusion. Ten units of oxytocin were placed in 500 ml of 0·9% saline and the infusion started at 2 milliunits per minute (mU/min). The oxytocin infusion rate was doubled automatically every 15 min until contractions were occurring three times in 10 mins or until a maximum infusion rate of 32 mU/min was achieved. For women whose labours were unusually slow the oxytocin infusion rate was increased to 64 or to 128 mU/min provided the fetal heart rate trace remained normal. Vaginal examinations were performed every 4 h to assess the progress of labour. There was no fixed protocol concerning the timing of the first vaginal examination: in some women it was performed soon after the initial speculum examination as a 'baseline', while in others it was delayed for 4 h after the start of regular painful contractions.

### *Conservative policy*

Women randomized to conservative management were sent to the antenatal ward to await the onset of labour. A qualified midwife was always on duty to observe the woman closely. If painful regular contractions supervened the fetal heart rate was monitored in the antenatal ward electronically with an external transducer. The woman was sent back to the labour ward if the fetal heart rate trace was worrying or when she wanted to have analgesia.

If labour had not supervened by the following morning induction of labour with an oxytocin infusion was performed, the infusion regimen being the same as for the actively managed group. Thus the conservative policy was not actually a true conservative policy; rather it was a policy of delayed oxytocin administration. There were two reasons for this:

(a) We were afraid of the possibility of serious intrauterine infection with very prolonged rupture of the membranes.

(b) We considered that in view of the risk of infection women in the conservative group should stay in the hospital, and that many would object if they felt that this stay were unduly prolonged.

The timing of the induction was determined by Table 2, a copy of which was kept in the labour ward. Thus induction of labour may take place at any time from 9 to 33 h after admission with prelabour rupture of the membranes. Table 2 was easily understood by the staff caring for the patient and did not lead to any ambiguities over the timing of formal induction, nor to induction of labour being undertaken at awkward times of the day.

Women in the conservative group had their axillary temperature taken every 6 h; if it reached ≥37·1°C labour was induced.

Women who were parous, who were in labour or who were preterm were excluded from the trial. A complete list of exclusions appears in Table 3.

The onset of labour was defined as regular contractions occurring twice in 10 min, detected by the hand of the midwife.

There is a low incidence of maternal and fetal infections in the hospital, and a low incidence of infection due to the β haemolytic streptococcus, Lancefield's Group B. It is therefore

**Table 2.** Timing of oxytocin administration in women allocated to the conservative policy

| Date and time of prelabour rupture of the membranes | Date and time of induction of labour |
|---|---|
| 1/11/85 at 0900 | 2/11/85 at 0900 |
| 1/11/85 at 2100 | 2/11/85 at 0900 |
| 1/11/85 at 2355 | 2/11/85 at 0900 |
| 2/11/85 at 0005 | 3/11/85 at 0900 |

**Table 3.** Trial of prelabour rupture of the membranes in term primigravidae—exclusions

| *Reasons for exclusion* |
|---|
| Multigravidae |
| Gestational age ≤36 weeks |
| Speculum examination revealed no amniotic fluid in the vagina |
| Contractions occurring once in 10 min or more often |
| Meconium-stained amniotic fluid |
| Multiple pregnancy |
| Breech presentation |
| Abnormal fetal heart rate trace on admission |
| Pre-eclampsia |
| Known or suspected intrauterine growth retardation |
| Diabetes mellitus |
| Any other significant medical disorder of pregnancy |

not routine policy to take high vaginal swabs at the time of the initial speculum examination in women admitted with prelabour rupture of the membranes. Prophylactic antibiotics were not prescribed to the mother nor to the infant, unless the mother was known in pregnancy to carry Group B streptococcus. Maternal pyrexia was defined as an axillary temperature of >37·1°C on one or more occasions during labour or the puerperium. Neonatal infection was assessed by consultant paediatricians who were not aware of the treatment allocations.

The hypothesis being tested by the trial is that the conservative policy will result in fewer caesarean sections by allowing time for the uterus to prepare for labour, that is by allowing time for biochemical and biophysical changes to occur which will maximize the efficiency of labour. The standard management in the hospital of primigravidae admitted with prelabour rupture of the membranes, other than in this trial, was an immediate oxytocin infusion. A pilot study showed that the caesarean section rate with this policy is 18%. In order to be able to demonstrate a reduction of this section rate by one half, to 9%, 440 women would have to be randomized ($\alpha = 0{\cdot}05$; $1-\beta = 0{\cdot}80$). The randomization process was by simple randomization without blocking from a table of random numbers.

**Table 4.** Characteristics of the women entered into the trial

| Variable | Conservative ($n = 225$) | Immediate oxytocin ($n = 219$) |
|---|---|---|
| Age (years) | 23·7 (3·9) | 24·2 (4·4) |
| Stature (cm) | 160·4 (6·6) | 159·5 (6·4) |
| Gestational age (weeks) | 39·3 (1·3) | 39·4 (1·3) |
| Birthweight (kg) | 3·32 (0·41) | 3·33 (0·46) |
| Time from membrane rupture to recruitment (h) | | |
| Median | 2 | 2 |
| Range | 0–48 | 0–18 |
| Interquartile range | 1–3 | 1–4 |
| Latent period (h) | | |
| Median | 12 | 5 |
| Interquartile range | 7–22·5 | 3–8 |

Results are mean (SD) values where appropriate.

### *Statistical methods*

Odds ratios (OR) and 95% confidence intervals (CI) were calculated for categorical outcomes. The number of vaginal examinations was considered as a continuous variable. A Shapiro-Francia W' test (Royston 1983) showed that the distributions of the number of vaginal examinations in each group were compatible with a Normal distribution. The significance of the difference between the number of vaginal examinations in the two groups was determined by a two-sample $t$-test, and the 95% CI of the difference estimated. Length of labour was not compatible with a Normal distribution, even after logarithmic transformation. The significance of the difference between the lengths of labour in the two groups was determined by the Mann Whitney $U$-test. The medians, interquartile ranges and the 95% CI of the medians in the two groups was estimated as described by Gardner & Altman (1989).

## Results

The trial took place between November 1985 and February 1991 in a single maternity hospital responsible for the care of about 4000 women each year. Overall 444 women were recruited, 225 being allocated to the conservative group and 219 to the oxytocin group. All 225 women in the conservative group were managed according to the conservative protocol, and 204/219 (93·2%) of those in the immediate oxytocin group were managed according to the oxytocin protocol. Fifteen women (6·8%) in the immediate oxytocin group were managed conservatively; in each case this was because the labour ward was too busy to undertake supervision of an oxytocin infusion. These women were kept in the immediate oxytocin group for analysis. Three envelopes could not be accounted for; these women had all been allocated immediate oxtyocin.

The baseline characteristics of the two groups are summarized in Table 4, which shows that the groups are alike as regards age, stature, gestational age and birthweight. Figure 1 is a relative cumulative frequency diagram of the proportions of women in each group achieving labour after spontaneous rupture of the membranes over each 6 h period. This shows that the time from the spontaneous rupture of the membranes to the onset of labour (the latent period) of some women in the immediate oxytocin group was long because they chose to stay

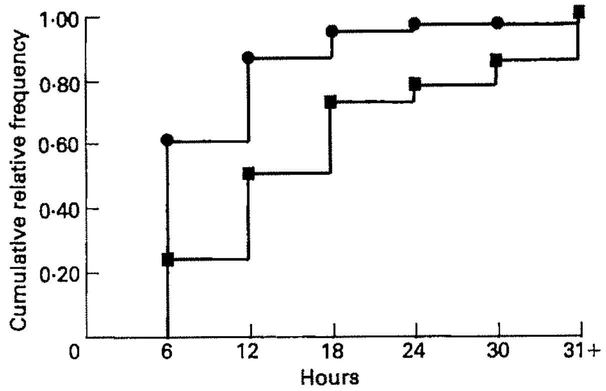

**Fig. 1.** Cumulative relative frequency diagram of latent periods. ■——■, conservative; ●——●, immediate oxytocin.

at home for some hours after prelabour rupture of the membranes. Table 4 shows that the median (interquartile range) latent period was 12 h (7–22·5 h) in the conservative group, and 5 h (3–8 h) in the immediate oxytocin group. Thus the trial design resulted in two groups of women who differed only in their latent periods.

In the conservative group, 171 (76%) women went into labour spontaneously, the rest requiring induction of labour. Of the women who achieved spontaneous labour, 78 underwent augmentation of labour with an oxytocin infusion; thus 93 women (41·3%) did not have an oxytocin infusion either for induction or for augmentation of labour.

Table 5 shows the main outcome of the trial, the mode of delivery. Women managed conservatively had fewer caesarean sections, the rate in the conservative group being 11·1% compared with 17·4% (OR 0·60; 95% CI 0·35 to 1·02; *P* = 0·06) in the immediate oxytocin group. A similar number of women in each group were delivered by forceps; but more women managed conservatively achieved a spontaneous delivery: nearly two-thirds of the women managed conservatively achieved a spontaneous delivery compared with just over one half of the women in the immediate oxytocin group (OR 1·57; 95% CI 1·08 to 2·29; *P* = 0·02).

The trial can give only a crude estimate of the optimum latent period. The median latent period in the conservative group was 12 h. There were 29 women in the oxytocin group who had latent periods of ≥12 h; 15 of these women were allocated to immediate oxytocin but owing to overwork in the labour ward they were managed conservatively, and an additional 14 women in the immediate oxytocin group chose to stay at home for several hours after prelabour rupture of the membranes occurred. A Mantel Haenszel estimate of the odds ratio of caesarean section where the latent period is ≥12 h, adjusting for the treatment allocation, shows that the OR (95% CI) is 0·55 (0·29 to 1·05); *P* = 0·06. This suggests that the optimum latent period is in excess of 12 h.

Table 6 summarizes the other outcomes studied in the trial. There was no differences in the lengths of labour between the two groups.

More women in the conservative group required no analgesia in labour or nitrous oxide only (OR 2·88; 95% CI 1·46 to 5·68; *P* = 0·003); a similar proportion had pethidine analgesia, while fewer women in the conservative group required epidural analgesia (OR 0·57; 95% CI 0·39 to 0·84; *P* = 0·005).

Women in the conservative group had fewer vaginal examinations (difference between means 0·53; 95% CI 0·25 to 0·80; *t* = 3·827; *P* <0·001). Fewer women in the conservative group had four or more vaginal examinations in labour (OR 0·58; 95% CI 0·39 to 0·86; *P* = 0·007).

There was no difference in the incidence of maternal pyrexia in labour or the puerperium, and a similar number of women in each group required antibiotics for actual or supposed infection. There was no difference in the number of infants given antibiotics. All the infants given antibiotics had superficial infections except one. This infant, whose mother had been allocated to conservative management, collapsed on the second day of life from pneumococcal septicaemia; the infant recovered with antibiotics. There were no perinatal deaths.

## Discussion

### *Mode of delivery*

This trial shows that there are considerable benefits in the policy of delayed administration of oxytocin to primigravidae admitted with prelabour rupture of the membranes. The policy results in fewer caesarean sections and more spontaneous deliveries, suggesting that the trial hypothesis is correct and that biological changes do occur during the latent period which favour efficient labour and spontaneous vaginal delivery. The optimum latent period is more than 12 h, but it is not possible from this trial to provide a more precise estimate. This should come from a large observational study in which the proportions of women in each 6 h latent period being delivered by caesarean section are estimated.

### *Analgesia*

The trial provides evidence that women managed conservatively had less painful labours. All the women in the conservative group who had only nitrous oxide and oxygen for analgesia had a similar story: admitted to the hospital with prelabour rupture of the membranes, randomized to conservative care, sent to the antenatal ward and brought back down later to the labour ward in spontaneous labour when a vaginal examination showed that they were about to deliver—in other words most of their labour had been accomplished relatively painlessly in the antenatal ward. All of these women achieved a spontaneousl vaginal delivery. More women managed actively had epidural analgesia, and this may be due to the fact that women having an oxytocin infusion in a labour ward are more likely to be offered an epidural block that those initially in an

**Table 5.** Outcome of the trial—mode of delivery

| | Conservative (*n* = 225) | Immediate oxytocin (*n* = 219) | Odds ratio | (95% CI) | *P* |
|---|---|---|---|---|---|
| Mode of delivery | | | | | |
| Caesarean section | 25 (11·1%) | 38 (17·4%) | 0·60 | (0·35 to 1·02) | 0·06 |
| Forceps | 59 (26·2%) | 68 (28·6%) | 0·79 | (0·52 to 1·19) | 0·26 |
| Spontaneous vaginal | 141 (62·7%) | 113 (51·6%) | 1·57 | (1·08 to 2·29) | 0·02 |
| Caesarean section rate and latent period | | | | | |
| | ≥12 h | <12 h | | | |
| Conservative | 9/112 (8·0%) | 16/113 (14·2%) | | | |
| Oxytocin | 3/29 (10·3%) | 35/190 (18·4%) | 0·55 | (0·29 to 1·05) | 0·06 |

**Table 6.** Outcome of trial—other end-points

| | Conservative | Immediate oxytocin | Odds ratio | (95% CI) | *P* |
|---|---|---|---|---|---|
| Length of labour (h) | | | | | |
| Median | 8 | 9 | | | |
| Interquartile range | 5, 13 | 6, 12 | | | |
| 95% CI of median | 8, 10 | 8, 10 | | | 0·40 |
| Analgesia | | | | | |
| Nitrous oxide only | 27 (12·0%) | 9 (4·1%) | 2·88 | (1·46 to 5·68) | 0·003 |
| Pethidine | 69 (30·7%) | 56 (25·6%) | 1·29 | (0·85 to 1·94) | 0·23 |
| Epidural | 129 (57·3%) | 154 (70·3%) | 0·57 | (0·39 to 0·84) | 0·005 |
| Vaginal examinations (*n*) | | | | | |
| Mean (SD) | 2·84 (1·36) | 3·37 (1·42) | t = 3·827 | | <0·001 |
| 95% CI of difference between means | | | | (0·25 to 0·80) | |
| ≥4 examination | 62 (27·6%) | 87 (39·7%) | 0·58 | (0·39 to 0·86) | 0·007 |
| Maternal infection | | | | | |
| Pyrexia | 84 (37·3%) | 91 (41·6%) | 0·84 | (0·57 to 1·23) | 0·36 |
| Antibiotics | 19 (8·4%) | 15 (6·8%) | 1·25 | (0·62 to 2·52) | 0·53 |
| Neonatal outcome | | | | | |
| Antibiotics | 12 (5·3%) | 7 (3·2%) | 1·68 | (0·67 to 4·22) | 0·27 |
| Serious infection | 1 | 0 | | | |
| Perinatal death | 0 | 0 | | | |

antenatal ward who are brought down to the labour ward in labour. However, the proportion of women randomized to conservative management who had epidural analgesia is similar to that of term primigravidae admitted to the hospital in spontaneous labour; the fact that the rate of epidural analgesia in the immediate oxytocin group is unduly high suggests that the oxytocin infusions resulted in unduly painful labours.

### *Vaginal examinations*

The greater number of vaginal examinations experienced by the women managed actively cannot be explained by the length of labour, since the length of labour was the same in each group. The explanation is partly the baseline vaginal examination which many of the women had who were randomized to immediate oxytocin and partly the policy of 4-hourly vaginal examinations which was rigidly adhered to in the labour ward. The women managed conservatively did not have a baseline vaginal examination for fear of introducing infection where the latent period might be long; also they experienced the early part of their labour in the antenatal ward where they did not have a vaginal examination. In fact there was probably no need for the baseline vaginal examination in the actively managed women, since no obvious harm occurred where it was not performed; and there was probably no need for a rigid protocol of vaginal examinations every 4 h in early labour, since the women managed conservatively who experienced the earlier part of their labour in the antenatal ward came to no harm.

### *Maternal and neonatal infections*

In retrospect the definition of maternal pyrexia was inappropriate. Many women sustained a single episode of raised axillary temperature in labour or the puerperium who did not have any evidence of infection. Many of these elevations of temperature were in association with epidural analgesia (Fusi *et al.* 1989). There was no evidence that a conservative policy resulted in a greater number of women requiring antibiotics for actual or supposed infection; furthermore it was reassuring that the overall need to prescribe antibiotics was small: only about 7% of women in the whole study were prescribed antibiotics.

The conservative policy did not have any apparent effect on the number of infants who received antibiotics. All of the neonatal infections were minor with the exception of the infant with pneumococcal septicaemia.

## Conclusions

This trial shows that the conservative policy has considerable advantages over induction of delivery with oxytocin infusion. However the trial has several limitations:

(a) The aetiology of prelabour rupture of the membranes is unknown but in some cases at least it is due to primary chorioamnionitis. We think that the incidence of primary chorioamnionitis is low in the population from which the samples for the study were drawn. In another population where primary chorioamnionitis is common and in particular where the prevalence of carriage of group B streptococcus is high, anxiety about serious infections due to prolonged spontaneous rupture of the membranes may outweigh concerns about high caesarean section rates. The results of this trial are only able to be applied to populations with a low rate of carriage of group B streptococcus.

(b) The trial is too small to comment on the effect of a conservative policy on serious neonatal infections. The incidence of serious neonatal infections in women with prelabour rupture of the membranes at term managed by an active policy is about

0·5% (Grant & Keirse 1989); in order to be able to detect a doubling of this incidence by a conservative policy, to 1%, approximately 9300 women would have to be randomized ($\alpha = 0{\cdot}05$; $1\text{-}\beta = 0{\cdot}80$). Serious neonatal infection is an important end-point of the management of prelabour rupture of the membranes, and a large multicentre trial should be undertaken.

(c) The trial was confined to primigravidae and the results may not therefore apply to multigravidae. Some multigravidae with prelabour rupture of the membranes may be at greater risk of cephalopelvic disproportion and the conservative policy, if it involves oxytocin administration, should be modified to take this into account.

(d) The study was of a shorter conservative policy and no comment can be made about the effectiveness or safety of a longer conservative policy, such as one where induction of labour is not performed and spontaneous labour is awaited in every case.

This trial shows that in term primigravidae with prelabour rupture of the membranes in whom the incidence of primary chorioamnionitis is low, a conservative policy, where induction of labour is delayed for at least 12 h, is to be preferred.

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FETAL AND NEONATAL MEDICINE

# Biochemical composition of amniotic fluid and extraembryonic coelomic fluid in the first trimester of pregnancy

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**ABSTRACT**

**Objective** To determine the biochemical composition of amniotic fluid and extraembryonic coelomic fluid between 8 and 12 weeks gestation.
**Design** Prospective observational study.
**Subjects** 40 women with a normal pregnancy between 7 and 12 weeks gestation having termination of pregnancy.
**Interventions** Before termination the women had a transvaginal ultrasound guided amniocentesis. Pure samples of amniotic fluid and extraembryonic coelomic fluid were obtained from each woman and standard biochemical variables were measured in each fluid sample immediately after collection.
**Results** Levels of sodium, potassium and bicarbonate were significantly higher in amniotic fluid whilst chloride, urea, bilirubin, protein, albumin, glucose, creatinine, calcium and phosphate were present in higher concentrations in extraembryonic coelomic fluid. All differences in concentration were significant ($P < 0{\cdot}05$; unpaired *t*-test). No relation was demonstrated between electrolyte concentrations in amniotic fluid or coelomic fluid and stage of gestation.
**Conclusions** Amniotic fluid and extraembryonic coelomic fluid have a widely differing biochemical composition. The biological significance of these differences remains unexplained.

Transvaginal ultrasonography allows detailed study of embryonic and early fetal development (Timor-Tritsch *et al.* 1988). It is possible to delineate the amniotic cavity from the surrounding coelomic fluid which contains the yolk sac (Figs. 1 and 2). Between 7 and 12 weeks gestation pure samples of amniotic fluid and coelomic fluid can be obtained using transvaginal ultrasound guided needling techniques (Wathen *et al.* 1991). Detailed information regarding the biochemical composition of these two fluid compartments in the first trimester is not presently available.

The aim of this study was to determine the concentrations of sodium, potassium, urea, chloride, bicarbonate, calcium, phosphate, creatinine, bilirubin, protein, albumin and glucose in samples of amniotic and coelomic fluid in early pregnancy.

## Materials and methods

Transvaginal ultrasound guided needle aspiration of samples of amniotic and coelomic fluid was performed on 40 women before termination of pregnancy at 7–12 weeks gestation. Consent was obtained in every case and the study was approved by the hospital ethics committee. Women with uncertain menstrual dates or vaginal bleeding were excluded from the study. Transvaginal ultrasound was performed using an Aloka SSD 620 with a 5 mHz vaginal probe (60 degree viewing angle). Gestational age was confirmed by measurement of crown rump length and fetal heart activity was identified in each case. Transvaginal ultrasound guided aspiration of amniotic and coelomic fluid was performed using an 18 gauge needle guide and a 22 cm 18 gauge needle with trocar (Casmed UK). The needle was guided through the vaginal vault and myometrium into either the extra-embryonic coelom or amniotic fluid, care being taken to avoid the placenta. In most cases coelomic fluid was aspirated before amniotic fluid. After collection of the first fluid sample the trocar was again introduced and the needle advanced into the second fluid compartment. The first 2 ml of fluid aspirated from the second sample was discarded to avoid contamination. It was noted that the coelomic fluid was straw

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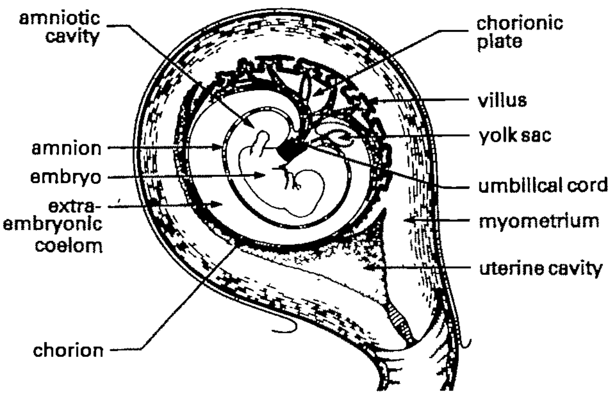

Fig. 1. Diagrammatic representation of an 8 week pregnancy showing the anatomical relation of the amniotic cavity and the extraembryonic coelom and other structures.

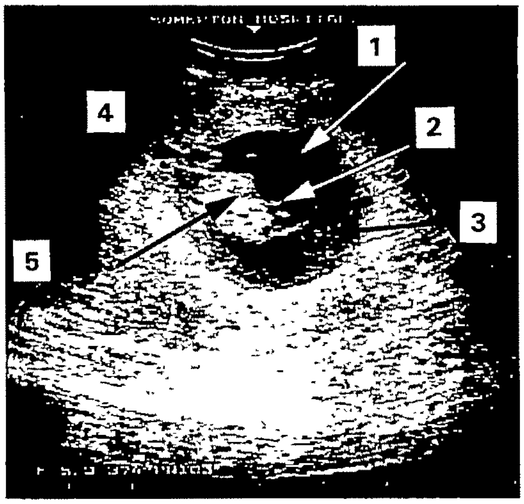

Fig. 2. Transvaginal sonographic picture of an 8 week pregnancy (1) amnion (2) amniotic cavity (3) extraembryonic coelom (4) yolk sac (5) embryo.

coloured and more viscous than the amniotic fluid, which was pale and clear. The electrolyte content of amniotic fluid and coelomic fluid was measured immediately after collection using an ERIS multichannel analyser (Merck, UK). Protein was measured using the Coomassie Blue Reagent (Bio-Rad Laboratories Ltd., UK) which was adapted for the ERIS analyser.

## Results

The results are presented in Table 1.

Statistical analysis was performed using the unpaired *t*-test on un-transformed data. When the composition of both fluids was compared, a significant difference in the concentration of sodium, potassium, chloride, urea, bicarbonate, creatinine, calcium, phosphate, bilirubin, protein, albumin and glucose was found. Sodium, potassium and bicarbonate were present in higher concentrations in amniotic fluid whilst all other items measured were higher in coelomic fluid. There was no significant difference in coelomic fluid. There was no significant difference in osmolality between the two fluids. No significant linear correlation was found between electrolyte concentrations in amniotic fluid or coelomic fluid and stage of gestation.

## Discussion

This is the first study in which standard biochemical variables have been determined in amniotic fluid and extra-embryonic coelomic fluid. The two fluid compartments have a widely differing composition. Levels of sodium, potassium and bicarbonate were higher in amniotic fluid. Chloride, urea, creatinine, calcium, phosphate, protein, albumin and glucose were higher in coelomic fluid. There were no significant changes in the constituents of the fluid compartments over the period of gestation studied despite alterations in fluid volume.

Extraembryonic coelomic fluid was present in greater quantities than amniotic fluid at 7 weeks gestation in all pregnancies examined. At 12 weeks gestation, however, extraembryonic

Table 1. Biochemical composition of amniotic fluid and extraembryonic coelomic fluid

| | Amniotic fluid | | | Coelomic fluid | | | Significance* | |
|---|---|---|---|---|---|---|---|---|
| Variable | *n* | Mean (SEM) | Range | *n* | Mean (SEM) | Range | *t* | *P* |
| Sodium (mmol/l) | 36 | 141·2 (0·25) | 139–144 | 32 | 138·1 (0·31) | 135–141 | 7·90 | <0·0001 |
| Potassium (mmol/l) | 36 | 3·98 (0·03) | 3·7–4·4 | 32 | 3·86 (0·03) | 3·5–4·2 | 3·0 | 0·0038 |
| Chloride (mmol/l) | 32 | 97·41 (1·1) | 83–111 | 24 | 110·1 (0·78) | 100–115 | –9·4 | <0·0001 |
| Urea (mmol/l) | 38 | 3·32 (0·14) | 2·0–5 4 | 34 | 3·9 (0·17) | 2·6–6·8 | –2 38 | 0·02 |
| Bicarbonate (mmol/l) | 37 | 34·24 (1·2) | 11–45 | 33 | 20·9 (0·56) | 16–29 | 9·98 | <0·0001 |
| Creatinine (µmol/l) | 40 | 37·1 (1·9) | 21–66 | 35 | 72·31 (6·6) | 32–264 | –5·13 | <0·0001 |
| Calcium (mmol/l) | 40 | 1·43 (0·07) | 0·86–2·57 | 32 | 2·66 (0·04) | 1·8–3·0 | –16·3 | <0·0001 |
| Phosphate (mmol/l) | 34 | 1·09 (0·1) | 0·47–2·84 | 28 | 2·69 (0·38) | 1·2–12·2 | –4·38 | <0·0001 |
| Bilirubin (µmol/l) | 24 | 0·64 (0·16) | 0–2·0 | 28 | 3·4 (0·38) | 0–9·0 | –7·05 | <0·0001 |
| Protein (g/l) | 29 | 0·97 (0·22) | 0–4·0 | 31 | 5·44 (0·44) | 2·9–14 | –9·09 | <0·0001 |
| Albumin (g/l) | 24 | 0·5 (0 20) | 0–3 0 | 27 | 4·63 (0·42) | 2·0–11 | –9·17 | <0·0001 |
| Glucose | 26 | 3·2 (0·1) | 2·5–4·2 | 19 | 3·7 (0·16) | 2·8–4·9 | –2·37 | 0 024 |
| Osmolality | 7 | 273·6 (1·57) | 268–280 | 5 | 270·6 (1·91) | 264–275 | 1·2 | 0·26 |

*Unpaired *t*-test.

coelomic fluid had nearly disappeared. The homeostatic mechanisms involved in controlling not only the biochemical content but also the volume of fluid at this stage of pregnancy remain unknown (Abramovich 1978).

The difference in composition of these two fluids may be partly explained by considering the anatomy of an early pregnancy (Hamilton *et al.* 1972). The extraembryonic coelom lies adjacent to the trophoblast and effectively surrounds the amniotic fluid which is separated from it by the amnion. The trophoblast, yolk sac, chorion and amnion should therefore exert more influence on the volume and composition of the coelomic fluid. Indeed coelomic fluid may be a transudate produced and secreted by the trophoblast and chorion from maternal serum. Amniotic fluid volume and composition will tend to be determined by the fetus, cord and amnion. Although the physiological processes involved in amniotic and coelomic fluid production remain unclear, it is believed that the amnion is involved in active secretion of fluid (McCarthy & Saunders 1978). Amniotic fluid may also arise by ultrafiltration of fetal serum through the fetal skin and cord (Lind 1978). The common barrier between the two fluids, the amnion, would seem to have an important role in maintaining biochemical differences between the two compartments. However, the biological significance of these differences remains unexplained.

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FETAL AND NEONATAL MEDICINE

# Clinical and histopathological features of parvovirus B19 infection in the human fetus

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## ABSTRACT

**Objective** To provide a comprehensive description of the clinical and histopathological features associated with parvovirus B19 infection of the human fetus.
**Subjects** All cases of parvovirus B19-related fetal death presenting to the John Radcliffe Hospital, Oxford, over a 16 year period. Diagnosis was confirmed retrospectively by non-isotopic *in situ* hybridization for parvovirus B19 DNA.
**Results** The ten cases occurred in two clusters (1979–80 and 1988–89) and presented between 15 and 29 weeks gestation. In at least three cases maternal infection was asymptomatic. Nine fetuses were grossly hydropic at necropsy. Histological features common to all cases included the presence of typical intranuclear inclusions in erythroid precursor cells and evidence of vasculitis within placental villi. Inflammatory changes were also present in the myocardium of four cases, with evidence of subendocardial fibroelastosis in three.
**Conclusions** Histological features of fetal parvovirus B19 infection are similar across a range of gestational ages. The heart failure and hydropic state associated with fetal parvovirus infection may be of multifactorial aetiology, and not due to fetal anaemia alone.

Human parvovirus B19 is the causative agent of the common childhood rash illness erythema infectiosum (Anderson *et al.* 1984) and is also a major cause of aplastic crises in patients with chronic haemolytic anaemias (Pattison *et al.* 1981). Infection with the virus was first shown to be associated with fetal death in 1984 (Brown *et al.* 1984; Knott *et al.* 1984). At least 60 such cases have been reported subsequently, the majority occurring during the second trimester and exhibiting generalized hydrops (see reviews by Rodis *et al.* 1988; Brown *et al.* 1989; Centres for Disease Control 1989). Parvovirus B19 has been shown to exhibit tropism for erythroid precursors *in vitro* (Ozawa *et al* 1987), and infection and lysis of these cells has been suggested to play an important role in the development of fetal anaemia, hydrops and death (Gray *et al.* 1987; Caul et al. 1988). A retrospective study from this laboratory has shown parvovirus infection to be the cause of four out of 13 cases of otherwise unexplained fetal hydrops (Porter *et al.* 1988a). Fetal death has occurred up to 12 weeks after maternal exposure to the virus (Bond *et al.* 1986), and may follow asymptomatic maternal infection (Brown *et al.* 1984; Carrington *et al.* 1987; Naides & Weiner 1989). Detailed histological findings have been presented in only nine isolated cases (Anand *et al.* 1987; Caul *et al.* 1988; Franciosi & Tattersall 1988; Maeda *et al.* 1988; van Elsacker-Niele *et al.* 1989; Katz *et al.* 1990), and the pathological processes underlying the development of hydrops in infected fetuses are incompletely understood.

There have been many reports of maternal parvovirus infection associated with a normal fetal outcome (see Kinney *et al.* 1988), although in only a few of these was there serological evidence of actual virus transmission to the fetus (Mortimer *et al.* 1985; Woernle *et al.* 1987; Public Health Laboratory Service Working Party on Fifth Disease 1990). At least 12 hydropic infants have survived following intrauterine transfusion (Schwartz *et al.* 1988; Peters & Nicolaides 1990; Southill 1990: Enders & Biber 1990; Sahakian *et al.* 1991), and we

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have recently reported that parvovirus B19 may be a cause of spontaneously resolving 'transient fetal hydrops' (Morey *et al.* 1991). It has not yet been determined why some infected fetuses develop fatal hydrops and others survive the infection.

Here we present the clinical details and pathological findings from a series of ten fetal deaths associated with parvovirus infection. Our results suggest that although infected fetuses exhibit similar histopathological abnormalities, the hydropic state itself may be of multifactorial origin.

## Subjects and methods

The ten fetal deaths reported in this study had been diagnosed retrospectively by non-isotopic *in situ* hybridization for parvovirus B19 DNA in a study of all cases of unexplained, anatomically normal fetal hydrops presenting to the Paediatric Pathology Department, John Radcliffe Hospital, Oxford between 1973 and 1989. The *in situ* hybridization method and diagnosis of four of these fetal deaths has been reported previously (Porter *et al.* 1988a), and an analysis of the tissue and cellular distribution of parvovirus B19 DNA in these cases is presented elsewhere (Morey *et al.* 1992)

Clinical details were obtained from the medical records of the eight hydropic fetuses born at the John Radcliffe Hospital, Oxford, and from referral requests and subsequent correspondence in the other two. Initial microscopic examination had suggested a viral cause of hydrops in eight, and of parvovirus in particular in another three, but in only one case (no. 4) was the possibility of parvovirus infection raised before delivery. Haematoxylin and eosin stained sections from all available tissues from each case were re-examined. The tissues including lung ($n = 9$), liver ($n = 8$), placenta/membranes/cord ($n = 10$), heart ($n = 6$), kidney/adrenal ($n = 8$), thymus ($n = 5$), spleen ($n = 5$), pancreas ($n = 2$), intestine ($n = 2$), diaphragm ($n = 2$), brain ($n = 3$) and rib/bone marrow ($n = 3$). Sections of heart were also stained with Orcein for elastin fibres, and sections of liver were stained with Perl's Prussian blue reaction for ferric iron. In order to assess the significance of this iron staining, liver sections from eight cases of fetal hydrops due to chromosomal or vascular abnormality were also stained in an identical manner.

## Results

A summary of the clinical history and presenting features of each case is presented in Table 1. Macroscopic and relevant microscopic abnormalities are summarized in Table 2. Cases are listed in order of increasing gestational age, as estimated from measurements of fetal crown-rump and foot length at necropsy.

### *Clinical features*

The ten cases occurred in two clusters: 1979–80 (five cases) and 1988–89 (five cases). These years coincide with outbreaks of erythema infectiosum in the United Kingdom detected in serological surveys (Dr B. Cohen, personal communication), though no cases were identified during a third outbreak of erythema infectiosum in 1985–86. No particular seasonal distribution was evident. Gestational age at presentation ranged from 15 to 29 weeks. The most common reason for admission was loss of fetal movements (five cases); one case presented with a raised maternal serum alpha-fetoprotein (AFP) level and another presented with severe pre-eclampsia. Fetal and placental oedema were seen at ultrasonographic examination in eight cases; in three of them fetal ascites was also evident. In all ten pregnancies abortion was subsequently induced with prostaglandin, with or without oxytocin. Serological studies for parvovirus were performed in three cases. In only one of them (no. 4, in which serum was obtained 3 weeks before delivery) was parvovirus-specific maternal IgM unequivocally detected; in another (case 1), serum obtained 6 weeks after delivery had an equivocal IgM titre, and in the third (no. 5), serum taken at delivery was negative. A lack of parvovirus-specific maternal IgM at the time of presentation with fetal hydrops has been reported by others (Caul *et al.* 1988; Peters & Nicolaides 1990) and presumably reflects a prolonged period between exposure to the virus and the development of hydrops.

No evidence of infection with any other agent was found. As far as can be determined, only one of the women had an illness involving a rash during pregnancy, though another five had reported non-specific influenza-like illnesses between 3 and 19 weeks before presentation. One was a teacher and another had six young children; the remainder were not in occupations associated with particular risk of exposure to parvovirus B19.

One woman presented before fetal death (no. 4). Sequential ultrasound scans from 16 weeks gestation (booking) to 20 weeks (when the pregnancy was terminated on the grounds of fetal non-viability) showed the development of ascites and increasing cardiomegaly. Scanning at the Pediatric Cardiology Unit at Guy's Hospital, London had suggested viral myocarditis as a possible cause of the poor cardiac contractility. Despite the progressive development of severe hydrops in this fetus, measurements of fetal growth increased appropriately for gestational age (see Table 1).

### *Pathological findings*

*Gross morphological features:* Seven of the ten fetuses had evidence of maceration. Nine fetuses were hydropic and had effusions in one or more body cavities as well as massive subcutaneous oedema. The least mature fetus (no. 1) had been observed to be mildly hydropic *in utero* by ultrasound examination, but this was no longer evident at necropsy 2 days later. Only one fetus (no. 6) exhibited dysmorphic features. These comprised a prominent forehead, beak-shaped nose with depressed nasal bridge and protruberent tongue. Transverse palmar creases were present bilaterally. Karyotyping was unfortunately unsuccessful. No fetus had evidence of any cardiovascular or visceral anomaly, though cardiomegaly was noted in no. 4. Several placentas were received in fragments rendering meaningful gross inspection impossible. Some of those which were complete were rather bulky, but not markedly pale or macroscopically hydropic.

*Histological features:* In nine fetuses, erythroid precursors with characteristic eosinophilic intranuclear inclusions and marginated chromatin were readily found in most tissues. These inclusion-containing cells often had a popcorn-like profile (Fig. 1), with blebs of basophilic material projecting from the surface. In three cases these intranuclear inclusions had

**Table 1.** Clinical history and presenting features

| No. | (Year) | Maternal age (parity) | Presentation | Symptoms of infection | Ultrasound findings | Serology/ virology |
|---|---|---|---|---|---|---|
| 1. | (1988) | 24 (0 + 0) | Abdominal swelling and fainting. Unaware of pregnancy. Laser treatment for CIN III 10 weeks before. Fundal height = 14 weeks | None reported | Hydropic fetus: No heart beat BPD = 2·8 cm (15 weeks) | TORCH and monospot –ve B19 IgG +ve and IgM equivocal 6 weeks after fetal death |
| 2. | (1988) | 28 (1 + 0) | Pain in r.groin. Tender uterus = 15 weeks | None reported | Fetal hydrops. Intrauterine death | TORCH –ve |
| 3. | (1980) | 20 (0 + 0) | Loss of fetal movements for one week at 24 weeks. Fundal height = 21 weeks | Two 'colds' at unspecified times during pregnancy | No fetal heartbeat. 'Halo' suggesting oedema. No ascites. Increased amniotic fluid. Bulky placenta ?Hydrops | TORCH, RSV mycoplasma, influenza and coxsackie all –ve |
| 4. | (1989) | 23 (0 + 0) | Raised MSAFP at 17 weeks (Amniotic fluid AFP normal [9·3 kU/ml] at 17 weeks; AchE gel test –ve) | 'Influenza' early in 4th month | 1. At booking: BPD = 3·2 cm, femur = 19 mm (16 weeks)<br>2. On presentation: active; BPD = 3·7 cm, femur = 20 mm (17 weeks); ascites, hepatomegaly, cardiomegaly with pericardial effusion.<br>3. Two weeks later (Guy's Hospital): heart dilated, poor contraction; no structural anomaly; viral myocarditis possible.<br>4. Three weeks later: active; BPD = 4·7 cm, femur = 26 mm (20 weeks); gross ascites with cardiomegaly and pericardial effusion; no pleural effusions | TORCH, listeria and toxoplasma –ve. Amniotic fluid and stool cultures –ve. B19 IgM +ve |
| 5. | (1989) | 28 (0 + 0) | Loss of fetal movements at 24 weeks | Viral illness with prolonged lethargy in first trimester | Intrauterine death. Oedema. Hydramnios. Large oedematous placenta | TORCH –ve. B19 IgM –ve |
| 6. | (1989) | 26 (1 + 0) | Referred as 'intrauterine death' at 25 weeks | None noted. Threatened miscarriage at 8 weeks | Intrauterine death | |
| 7. | (1980) | 30 (0 + 2) | Loss of fetal movements at 25 weeks | Rubella-like illness at 15 weeks (rubella serology –ve then) | Intrauterine death. Size = 20 weeks. Collapsed head, transonic areas in chest and abdomen ? ascites. Bulky placenta | TORCH –ve |
| 8. | (1979) | 30 (6 + 0) | Loss of fetal movements for 10 days at 26 weeks. Fundal height = 24 weeks | Backache, legache and fatigue at 12 weeks. MSAFP normal at 15 weeks | Intrauterine death. BPD = 5·8 cm (22–3 weeks). Double imaging of skull, and ?ascites. Bulky placenta | Rubella –ve, CMV –ve |
| 9. | (1979) | 23 (1 + 1) | Loss of fetal movements for one month at 29 weeks and weight loss of 2 kg. Fundal height = 26 weeks | 'Influenza' in third month | Intrauterine death. BPD = 22–3 weeks. Very collapsed head; large pocket of gas in abdomen. Bulky placenta | |
| 10. | (1979) | 30 (2 + 0) | Severe pre-eclampsia with pulmonary oedema at 29 weeks. Fundal height = 33 weeks | 'Flu-like illness after contact with child with 'rubella' at 10 weeks (rubella serology –ve) | No fetal heartbeat or movements. Gross fetal oedema. Very bulky placenta. No hydramnios. BPD = 6·6 cm | |

Abbreviations: CIN = cervical intraepithelial neoplasia, BPD = biparietal diameter; MSAFP = maternal serum alpha-fetoprotein; AchE = acetylcholinesterase; RSV = respiratory syncitial virus; CMV = cytomegalovirus.

**Table 2.** Macroscopic and microscopic fetal abnormalities (in addition to the presence of viral inclusions)

| No. | (Sex) | Gestational age (weeks) | Gross Findings | Placenta | Lung | Heart | Other |
|---|---|---|---|---|---|---|---|
| 1. | (F) | 14 | Macerated. Not obviously hydropic | Intervillous fibrin and leucocytosis. Patchy hydropic change. Vasculitis in stem arteries, villous capillaries and cord. Villous arteritis | | Some swollen myocyte nuclei. Nuclear debris++ | |
| 2. | (M) | 15 | Macerated. Marked subcutaneous oedema. Pallor of all organs | Intervillous fibrin and patchy hydropic change. Round cell infiltration of villous stroma and vasculitis | Nuclear debris++ in alveoli | | Hassall's corpuscles present in thymus |
| 3. | (F) | 18 | Macerated. Generalized oedema with ascites and pleural effusions | Intervillous fibrin. Not hydropic. Focal stem arteritis, vasculitis and villitis. Nuclear debris ++. Neovascularization of capillaries | Thickened alveolar walls with round cell infiltrate | | |
| 4. | (M) | 19 | Generalized oedema with ascites and cardiomegaly | Intervillous fibrin and leucocytosis. Stem arteritis, villitis and vasculitis. Marked decidualitis | Thickened alveolar walls with round cell infiltrate | Subendocardial fibro-elastosis of ventricles. Focal round cell infiltrate | Reduced cortical lymphocytes in thymus with well-formed Hassall's corpuscles |
| 5. | (F) | 20 | Very macerated. Pleural effusions and ascites | Intervillous fibrin and patchy hydrops. Vasculitis. Debris ++ in villous stroma with round cell infiltrate | Rather autolysed. Debris in stroma | Very autolysed | |
| 6. | (F) | 23 | Generalized oedema. Small pleural and pericardial effusions. Minor facial dysmorphology Transverse palmar creases | Intervillous fibrin. Round cell infiltrate in villous stroma. Vasculitis of villi and stem arteries. Perivascular nuclear debris in villi | Rather autolysed. Abnormal cells in alveolar lining++ | Very autolysed | |
| 7. | (M) | 24 | Generalized oedema. Pleural and pericardial effusions. Marked ascites | Intervillous fibrin and leucocytosis. Patchy hydrops. Nuclear debris in villous stroma. Decidualitis | Interstitial round cell infiltrate. Abnormal cells in alveolar lining++ | Minor subendocardial fibro-elastosis. Round cell infiltrate | Petechial haemorrhages in brain with focal round cell infiltrates in Virchow-Robin's space. Cellular leptomeninges |
| 8. | (F) | 24 | Macerated++ Oedema of limbs and distension of abdomen by ascites | Intervillous fibrin and patchy hydrops. Nuclear debris in villous stroma. Vasculitis. Chorangiosis | Abnormal cells in alveolar lining | | Well formed Hassall's corpuscles in thymus |
| 9. | (M) | 26 | Macerated. Subcutaneous oedema++ Ascites and small pleural effusions | Intervillous fibrin and calcification of villous stroma. Stem artery sclerosis and patchy thrombosis with recanalization. Vasculitis and mixed inflammatory cell infiltrate | Abnormal cells in alveolar lining | | |
| 10. | (M) | 29 | Macerated. Generalized oedema and ascites | Intervillous fibrin and leucocytosis. Focal villitis and vasculitis. Chorangiosis | Abnormal cells in alveolar lining++ | Some swollen myocyte nuclei. Round cell infiltrate and minor endocardial fibro-elastosis | Well formed Hassall's corpuscles and cortical lymphocyte depletion in thymus |

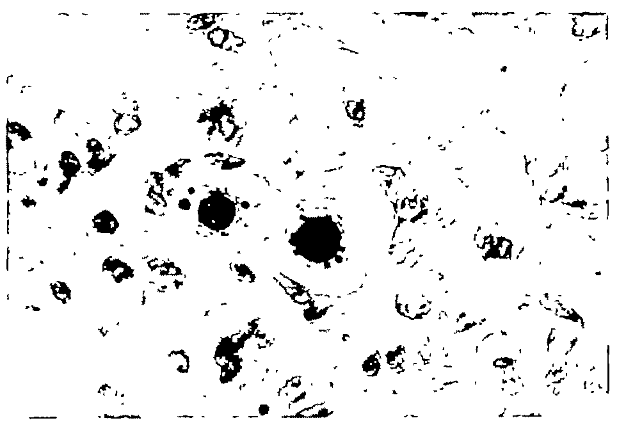

**Fig. 1.** Two typical parvovirus inclusion cells with marginated chromatin in a myocardial capillary (case 10). Protrusions of basophilic material give the cells a 'popcorn like' appearance Hamatoxylin & eosin stain (magnification ×1070). See also Fig. 4.

been noted and identified as probable viral inclusions before the first report of their significance in fetal parvovirus infection by Burton (1986). As noted by Burton & Caul (1988), inclusion-containing cells appeared relatively resistant to autolysis and could be detected even when there was marked autolytic change following intrauterine death. The majority of cells containing these inclusions clearly lay within blood vessels and capillaries, though they were also found in extramedullary haemopoietic foci in the liver, adrenal and thymus. The number of these characteristic cells varied between tissues and fetuses from <1 to >20 per high power field. They were generally most frequent in the liver (the major site of erythropoiesis in early second trimester), moderately frequent in the lung (often the best preserved tissue), but relatively infrequent in the brain and placenta. In the most mature fetus (no. 10), greater numbers of these cells were seen in the bone marrow than the liver, a finding consistent with the changing pattern of erythropoiesis with increasing gestational age. In all but one case (no. 4) there was also an apparent increase in the number of normal circulating nucleated erythroid cells. In case 4, typical parvoviral inclusions were extremely rare and were only detected after meticulous examination of the tissues. *In situ* hybridization studies for parvoviral DNA had revealed less than one positive cell per high power field in most tissues from this case, unlike tissues from the other nine cases which generally contained vast numbers of positive cells (Morey *et al.* 1992).

In the majority of tissues the only histological abnormality was the presence of numerous inclusion-containing cells. Tissues in which this was the case (such as kidney and adrenal) have been excluded from Table 2 which summarizes additional abnormalities found in blocks of placenta, lung, myocardium, thymus and brain.

Pathological features were present in the placentas of all ten cases Intervillous fibrin and intervillous leucocytosis were common, and patchy hydropic change was seen in half the cases. The most striking abnormality was a vasculitis affecting villous capillaries and in some cases, stem arteries as well. Affected vessels exhibited swelling of endothelial cells, fragmentation of endothelial cell nuclei and fibrin thrombi. Perivascular, predominantly mononuclear, inflammatory cells and nuclear debris were common (Fig. 2). In two of the older fetuses villous capillaries were very peripherally sited and more numerous than expected for gestational age (chorangiosis) and in case 3 there was evidence of recanalization of thrombosed capillaries. Marked inflammatory infiltration of the decidua was also present in two cases (Fig. 3). Seen together, these changes suggest that inflammation within the placenta is a common feature of fetal parvovirus infection in the second trimester.

Interestingly, vasculitis and perivascular inflammation were not consistent findings in other organs, though interstitial round cell infiltrates were seen in the lungs of three fetuses. Alveolar walls were thickened by oedema fluid, and large cells with swollen nuclei were located at the alveolar margin in the five most mature fetuses (Fig. 4). These cells had marginated chromatin, but lacked the typical eosinophilic nuclear inclusions characteristic of parvovirus B19-infected normoblasts.

Round cell infiltrates were present in the myocardium of four cases (Fig. 5). In cases 1 and 10 occasional myocyte nuclei were also abnormally swollen. The fetus which had shown evidence of cardiomegaly and poor cardiac contractility on ultrasound examination (no. 4) had histological evidence of marked focal fibro-elastosis beneath the ventricular endocardium, demonstrated by strong staining for elastin (Fig. 6), a fea-

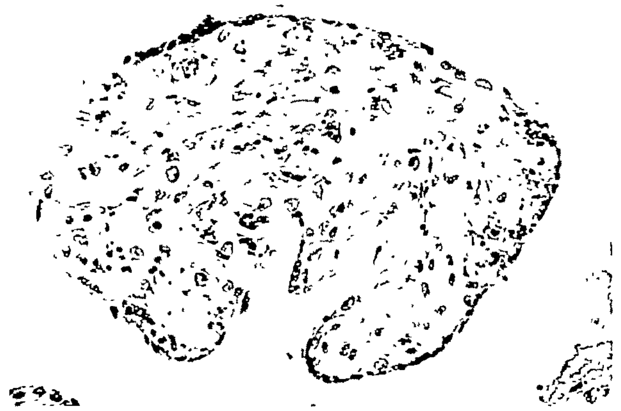

**Fig. 2.** Round cell infiltration and nuclear debris within a placental villus (case 5). Haematoxylin & eosin stain (magnification ×425).

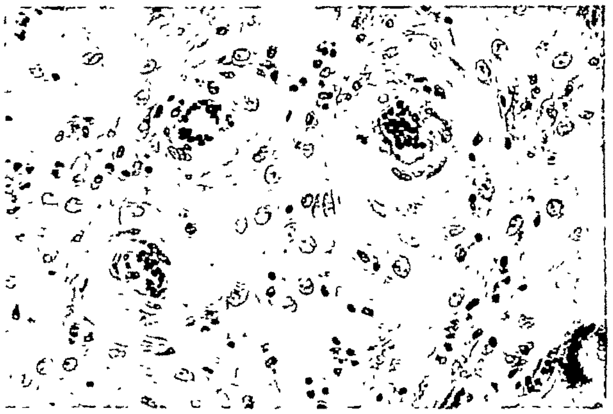

**Fig. 3.** Round cell infiltrate within the placental decidua (case 4). Haematoxylin & eosin stain (magnification ×265).

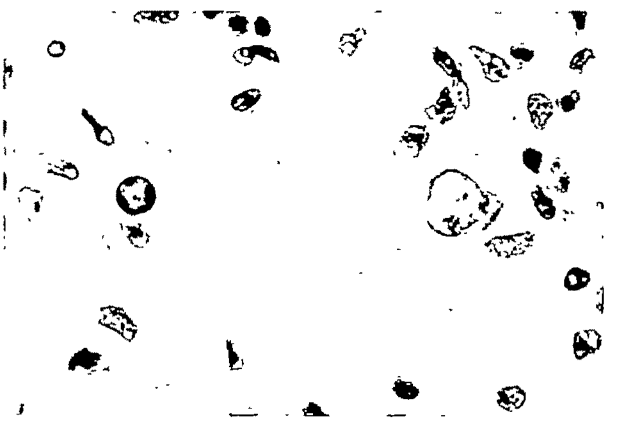

Fig. 4. Typical parvovirus inclusion cell (centre left) contrasted with a large abnormal cell in the alveolar lining (centre right) (case 8). Though having marginated chromatin, these alveolar cells lacked central eosinophilic inclusions and their identity could not be determined with certainty. Haematoxylin & eosin stain (magnification ×1070).

ture which was also present to a lesser degree in cases 7 and 10. Myocardial tissue from the two other available cases was too autolysed for meaningful examination.

In thymus from four of the five available cases development of Hassall's corpuscles was striking and appeared advanced for gestational age in terms of size and frequency. Cortical lymphocyte depletion, a feature suggestive of severe intrauterine stress, was seen in two of these cases. Brain tissue from one case showed round cell infiltration of the leptomeninges and scattered petechial haemorrhages, though the latter may have arisen during delivery.

Liver tissue from the eight available parvovirus-infected cases was too autolysed for detailed analysis of cellular morphology, but staining with Perl's Prussian Blue revealed the presence of considerable amounts of ferric iron in the liver in all cases. The iron was distributed in a uniform fashion (Fig. 7), apparently lying within both hepatocytes and Kupffer cells, and was most prevalent in the oldest fetuses. The amount of iron did not correlate with the number of infected cells in the liver, as determined by *in situ* hybridization (Morey *et al.*). Considerable ferric iron deposition was also found in the livers of five of the eight control cases of hydrops associated with chromosomal or abnormality, though the vascular amount of iron was generally somewhat less than in the parvovirus-infected cases and the pattern of distribution was distinctly different, being particularly marked in the periportal area. Interestingly, all five of these cases had proven Turners syndrome; no significant deposits of ferric iron were found in two cases of hydrops associated with Trisomy 21 or one secondary to twin-to-twin transfusion.

## Discussion

The ten cases of parvovirus-related fetal death described here form the largest reported series of such cases. They represent 27% of the cases of anatomically normal non-immune hydrops (8% of all cases of non-immune hydrops) presenting to the John Radcliffe Hospital, Oxford between 1973 and 1989.

It is evident from this and other studies that the presence or nature of maternal symptomatology in cases of parvovirus B19 infection during pregnancy bears no obvious relation to the development of fetal hydrops. Infection in at least three of the ten cases presented here was subclinical, a proportion similar to that in other case reports. A recent prospective study by the Public Health Laboratory Service Working Party on Fifth Disease (1990) examined the risk of fetal death due to parvovirus in pregnant women with proven infection; most of these women (91%) had presented with a rash. In such cases the risk of fetal death due to the infection was approximately 9%. Because of the prospective nature of the study, however, cases of fetal death shown retrospectively to be due to asymptomatic parvovirus infection were not included. The fetal loss rate in cases of asymptomatic infection is therefore unknown.

One of our patients presented with a raised maternal serum AFP level, supporting the hypothesis that elevation in the level of this protein may be an indicator of poor fetal prognosis in certain cases of intrauterine parvovirus infection (Carrington *et al.* 1987; Bernstein & Capeless 1989), although fetal death following normal serum AFP estimation has also been reported (Samra *et al.* 1989). In our case the amniotic fluid level of AFP, assayed shortly after the abnormally raised maternal serum AFP was detected on routine screening, was normal, suggesting that raised AFP levels in the maternal blood may represent excessive leakage across a damaged pla-

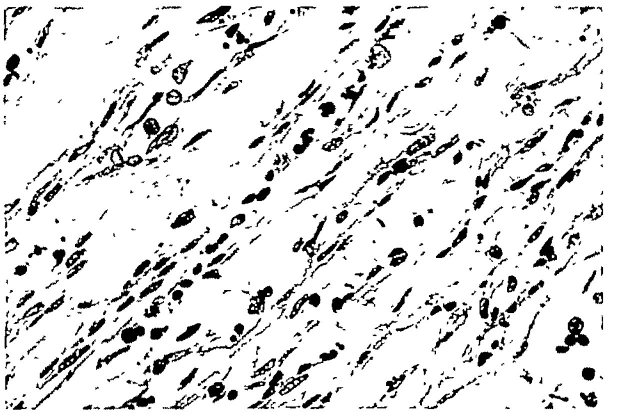

Fig. 5. Round cell infiltrate and nuclear debris in the myocardium (case 7). Haematoxylin & eosin stain (magnification ×425).

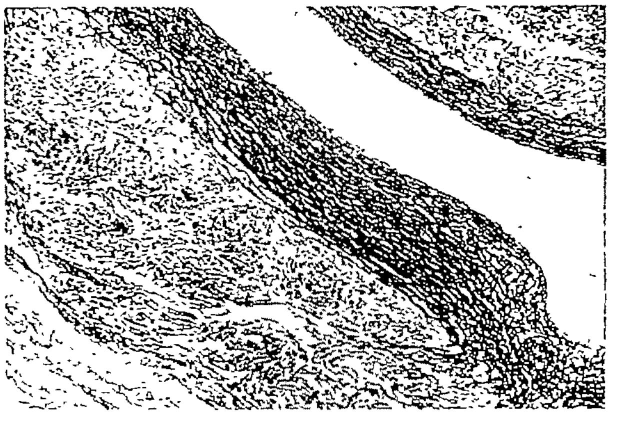

Fig. 6. Marked focal subendocardial fibro-elastosis demonstrated by staining for elastin (case 4). Orcein stain (magnification ×135).

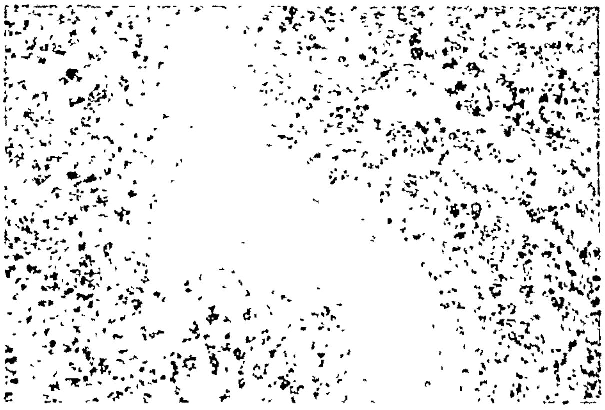

Fig. 7. Ferric iron deposition in the liver (case 10). Perl's Prussian blue reaction without counterstain (magnification ×170).

cental barrier. Another patient presented with severe pre-eclampsia. Similar clinical features have been reported in two other cases of fetal parvovirus B19 infection (Anand *et al.* 1987; Metzman *et al.* 1989) and although rapid-onset pre-eclampsia is a recognized complication of fetal hydrops (Gough *et al.* 1986), the mechanisms underlying the development of this condition in such cases are obscure.

Species-specific parvovirus infections are a widespread problem in veterinary practice; the predilection of this family of viruses for rapidly dividing cells has been shown to result in stillbirth, congenital malformations and neonatal death in a variety of animals (Siegl 1984). The possibility of teratogenic effects arising from human parvovirus infection has been investigated in a number of epidemiological studies with negative result (Ager *et al.* 1966; Mortimer *et al.* 1985; Kinney *et al.* 1988; Public Health Laboratory Service Working Party on Fifth Disease 1990) although one malformed embyro from a pregnancy complicated by parvovirus infection has been reported (Weiland *et al.* 1987). One fetus examined in the present study had minor dysmorphic features of face and hands. The gestational age at which the infection had occurred in this case could not be ascertained from the clinical information, and the likelihood of parvovirus B19 causing the observed abnormalities could not be assessed. However, fetal death occurred many weeks after the completion of embryogenesis.

The histological features of the ten cases reported here are in general agreement with the findings of others who have made detailed studies of cases of second trimester parvovirus-associated hydrops (Anand *et al.* 1987; Caul *et al.* 1988; Franciosi & Tattersall 1988; Maeda *et al.* 1988; Katz *et al.* 1990). Important additional features noted in the present study include the consistent presence of inflammatory changes within the placental vasculature, and inflammatory cell infiltration of the myocardium with subendocardial fibroelastosis in three cases.

Inflammation within the placenta has not been reported previously in cases of fetal hydrops secondary to parvovirus infection, though two cases of non-hydropic parvovirus B19-related fetal death from the Netherlands had perivascular infiltrates within the placenta (van Elsacker-Niele *et al.* 1989). Studies looking at the distribution of parvovirus virions within homogenized fetal tissues using electron microscopy have found the placenta to be the only tissue in which aggregates of virus with endogenous antibody are found (Bond *et al.* 1986; Carrington *et al.* 1987; Clewley *et al.* 1987). The rash and arthralgia typically associated with parvovirus B19 infection are generally thought to be secondary to immune complex deposition and it is possible that the inflammation seen within the placenta is a response to the deposition of virus complexed with maternal IgG that has crossed the placental barrier. Perivascular inflammation would also be expected if direct viral infection of the endothelium occurred. Swelling of endothelial cells and fragmentation of their nuclei were noted in the placental vessels, and some animal parvoviruses are known to have tropism for endothelial cells (Coleman *et al* 1983). However, we have been unable conclusively to demonstrate parvovirus B19 DNA within the fetal endothelium by *in situ* hybridization (Morey *et al.* 1992).

The identity of the abnormal swollen cells found in lung tissue from the five most mature fetuses is uncertain. They may be infected alveolar lining cells, or it is possible that they are giant infected erythroid precursors which have caused distension of capillaries with apparent 'prolapse' into the alveolar lumen. Unlike typical inclusion-containing cells, however, they failed to label consistently with monoclonal antibody to glycophorin A (data not shown), and definitive identification of these unusual cells awaits ultrastructural studies on well-preserved fresh material.

Our observations support the view that human parvovirus infection may result in severe damage to the fetal myocardium. Inflammatory changes were detected in four cases, and ultrasonographic findings had shown poor myocardial contractility in the one fetus that presented before death. Subendocardial fibro-elastosis was present in three of these four cases and occasional swollen myocyte nuclei were seen in two of them. Although some of these features may have resulted from hypoxia or ischaemia rather than direct myocardial infection, double label studies on these cases have detected parvovirus B19 DNA in occasional myocardial cells labelled with an antibody to desmin (Porter *et al.* 1988b & 1990; Morey *et al.* 1992). Case reports suggesting a major role for fetal myocarditis in the causation of parvovirus B19-related hydrops have also been presented by Naides & Weiner (1989) (who detected parvovirus-like particles in myocyte nuclei by electron microscopy) and Katz *et al* (1990) (who noted focal myocardial calcification). Histological evidence of myocarditis was also noted in an embryo with congenital eye abnormalities believed to result from B19 infection (Weiland *et al.* 1987). Endocardial fibro-elastosis has only recently been noted in a case of human fetal parvovirus infection (Newbould *et al.* 1991), although its association with fetal hydrops has been well described (Moller *et al.* 1966; Keeling *et al.* 1983; Newbould *et al.* 1991). This condition has also been reported to follow myocarditis in puppies infected with canine parvovirus (Levin 1980). Evidence is thus accumulating that infection of the myocardium may be an important feature of human fetal parvovirus infection.

Lysis of red cell precursors has been suggested as the underlying cause of hydrops associated with parvovirus infection (Caul *et al.* 1988). The evidence for this rests on the detection of large amounts of ferric iron in the livers of infected fetuses (Anand *et al* 1987; Caul *et al.* 1988). However, haemolysis has not been reported to be a feature of parvovirus infection in children or adults, and a normal bilirubin level has been reported in a cordocentesis sample from a severely anaemic infected fetus

(Sahakian *et al.* 1991). Although substantial deposits of ferric iron were found in the livers of parvovirus-infected fetuses in the present study, considerable iron deposition was also noted within the livers of five control cases of hydrops secondary to Turner's syndrome. This suggests that the accumulation of iron in the liver is not necessarily related to haemolysis, and in parvovirus-infected fetuses it may simply reflect reduced uptake by infected erythroid precursors, or generalized hepatic dysfunction. Abnormally elevated liver enzymes have been detected in serum from an infected fetus (Sahakian *et al.* 1991) and features suggestive of hepatocyte damage, such as ballooning degeneration, individual cell necrosis and periportal fibrosis, have been described in some other cases of parvovirus-related fetal death (Anand *et al.* 1987; Maeda *et al.* 1988; Metzman *et al.* 1989). Unfortunately the degree of hepatic autolysis present in all ten cases described here did not permit assessment of such features. However, double-label studies on tissues from these parvovirus infected fetuses have suggested that parvovirus B19 DNA-positive cells are frequently phagocytosed intact by macrophages in the liver (Porter *et al.* 1990; Morey *et al.* 1992). It is possible that in parvovirus infection widespread maturation arrest and phagocytosis of infected erythroid precursors (rather than lysis) are responsible for reducing the overall oxygen carrying capacity of the blood, leading to 'effective' anaemia in the presence of apparently robust compensatory erythropoiesis.

Possible mechanisms for the development of non-immune fetal hydrops have been discussed previously (Keeling *et al.* 1983). They include (i) chronic severe anaemia, leading to high output cardiac failure and hypoxic damage to the capillary bed producing increased capillary permeability, (ii) hypo-albuminaemia, resulting in reduced colloid osmotic pressure and allowing the escape of fluid into the extravascular compartment, (iii) intrauterine congestive cardiac failure secondary to direct myocardial damage, leading to increased capillary hydrostatic pressure, and (iv) obstructed venous return from the placenta. The rate of change of indices such as haemoglobin and serum protein levels, rather than the absolute levels, may also be of great importance. Fetal anaemia secondary to the infection of erythroid precursors undoubtedly plays an important role in the causation of parvovirus-induced hydrops, but there is evidence to suggest that all the above-mentioned mechanisms contribute. Protein leakage across endothelial and placental barriers damaged by hypoxia and immune complex deposition would be compounded by hypo-albuminaemia secondary to hepatic damage. Obstruction of venous return by massive ascites (Schwarz *et al.* 1988), extreme placental oedema or hepatic enlargement due to excessive extramedullary haemopoiesis could lead to cardiac decompensation and thus contribute to the hydropic state. Myocardial function would be compromised by inflammation within the myocardium, which could also lead to fibrosis, scarring and disturbance of the cardiac conduction system. We therefore suggest that fetal hydrops associated with parvovirus infection is multifactorial in origin. The possibility that direct myocardial damage is an important contributing factor certainly requires further investigation, particularly in view of the implications for the choice of fetal therapy, and potential long term sequelae if fetal death is averted.

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FETAL AND NEONATAL MEDICINE

# Long term predictive value of Doppler studies in high risk fetuses

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## ABSTRACT

**Objective** To determine whether the predictive value of Doppler ultrasonography extends beyond the perinatal period.
**Design** Descriptive follow-up study.
**Setting** Specially designated paediatric clinic in Royal Maternity Hospital
**Subjects** 40 children who as high risk fetuses had had assessment of umbilical artery flow velocity waveforms.
**Interventions** Parental history, physical examination, anthropometry, Denver developmental screening test.
**Outcome measures** Weight, height, head circumference, neurological impairment, Denver developmental screening test
**Result** Abnormal waveforms were an accurate predictor of neonatal outcome, with significant differences in birthweight, gestational age, need for nursery admission, and frequency of intrauterine growth retardation between normal and abnormal waveform groups. However, abnormal Doppler studies were not predictive of long-term adverse sequelae. There were no significant differences in height, head circumference, proportion with neurological impairment, or results of Denver developmental screening test at a median age of five years.
**Conclusion** The predictive value of Doppler ultrasonography is less for long-term growth and neurodevelopment than for perinatal outcome in the high risk fetus.

Doppler ultrasonography is being increasingly used in obstetric decision-making. It has been suggested that umbilical artery flow velocity waveforms might be used to screen unselected pregnant women for placental insufficiency (Redman 1989). Many reports have shown abnormal blood flow velocities to be a good predictor of adverse perinatal outcome in the high risk fetus, both in pregnancies complicated by intrauterine growth retardation (Erskine & Ritchie 1985; Trudinger *et al.* 1985; Burke *et al.* 1990; Hackett *et al.* 1987) and maternal hypertension (Trudinger & Cook 1990; Cameron *et al.* 1988). We have found no reports of prediction of outcome beyond the perinatal period.

The aim of our pilot study was to determine whether the prognostic value of Doppler ultrasonography extends beyond the perinatal period by studying growth and development in an appropriate group of children. This descriptive study has a small sample size, because the cohort of children were the subject of fetal assessment during the period 1984-1986, when the role of Doppler studies was being defined in this hospital.

## Subjects and Methods

The study group comprised 74 consecutive singleton high risk pregnancies referred to a hypertension antenatal clinic or admitted to hospital because of hypertension and/or suspected intrauterine growth retardation. Forty-one women had pregnancy-induced hypertension, 19 had chronic hypertension, three had chronic hypertension complicated by pregnancy-induced hypertension, and 11 had intrauterine growth retardation in the absence of hypertension.

All fetuses were assessed by ultrasonic scan, biophysical profile and Doppler ultrasonography at a median of two days before delivery. A range-gated pulsed Doppler Mark V Duplex Scanner (Advanced Technology Laboratories) was used to obtain umbilical artery flow velocity waveforms. The pulsatility index (PI) was then calculated (Gosling & King 1975) and abnormal umbilical artery flow velocity waveforms (i.e., those showing reduction, absence, or reversal of the diastolic waveform component) were defined as those having a PI level >2SD above the mean value for gestational age when compared with our own previously established normal range (Harper 1987). Small-for-gestational age babies were defined as those whose birthweight was less than the 10th centile for gestational age on the Gairdner & Pearson chart (Castlemead Publications Ltd, Herts.). Clinicians involved in obstetric decision-making and paediatric follow-up were unaware of the Doppler findings.

In the prospective arm of the study, 40 children were reviewed at a median age of 57 months (range 48–69). Of the 34 not reviewed, three were intrauterine deaths, three were neonatal deaths, one died in infancy, seven could not be traced because the families had left N. Ireland and in 20 children the

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**Table 1.** Perinatal outcome (frequency and relative risk) with normal and abnormal umbilical artery Doppler ultrasonography

| Outcome | Normal Doppler ($n = 40$) | Abnormal Doppler ($n = 34$) | Relative risk (95% C.I.) |
|---|---|---|---|
| Intrauterine death | 1 (3) | 2 (6) | 2·4 (0·2–24·8) |
| Neonatal death | 0 | 3 (9) | – |
| Emergency caesarean section | 7 (18) | 15 (44)* | 2·5 (1·2–5·8) |
| Gestational age (weeks) | 36·6 (2·5) | 32·1 (3·4)** | – |
| Birthweight (g) | 2689 (704) | 1363 (578)** | |
| Small-for-gestational age | 11 (28) | 28 (82)** | 3·0 (1·8–5·1) |
| Admitted to neonatal unit | 15 (38) | 30 (94)** | 1·8 (1·2–2·9) |
| Hypoxic-ischaemic encephalopathy | 1 (2) | 0 | – |
| Respiratory distress syndrome | 2 (5) | 8 (25)* | 4·7 (1·1–20·7) |
| Mechanical ventilation | 2 (5) | 9 (28)* | 5·3 (1 2–22·9) |
| Intraventricular haemorrhage | 0 | 2 (6) | – |
| Necrotizing enterocolitis | 1 (3) | 4 (13) | 4 7 (0·6–40 1) |
| Neonatal seizures | 0 | 1 (3) | – |
| Duration of hospital stay (days) | 10·9 (10·7) | 45·0 (31·4)** | – |

* $P<0{\cdot}05$, ** $P<0{\cdot}001$.
Results are mean (SD) or *n* (%) values as appropriate.

family declined to attend the follow-up clinic despite being invited on two occasions. Parental history, anthropometric measurements, physical examination and Denver developmental screening tests (Denver Developmental Materials Inc., Denver, USA) were performed.

Failure of the Denver developmental screening test was defined as two or more delays in two or more sectors of the revised test form. Seizures were recorded if they had occurred at any time after the neonatal period. Need for special school was defined as schooling within a unit attached to a primary school, or in a special school. Deafness was defined as sensorineural hearing loss sufficient to require a hearing aid. Visual handicap was defined as corrected visual acuity in the better eye of 4/60 to 6/24—that is, fulfilling criteria for registration as partially sighted—or blindness (worse than 4/60). Cerebral palsy was defined as a disorder of movement and posture (Stanley 1979). Squint was defined as a failure of both visual axes to direct to the same point of fixation. Height was measured with a stadiometer using a standard anthropometric technique and plotted on a Tanner and Whitehouse centile chart (Castlemead Publications Ltd). Occipito-frontal circumference (OFC) was estimated using a tape measure and plotted on a Nellhaus chart (Nellhaus 1968). Informed parental consent and approval from the Research Ethical Committee of the Queen's University of Belfast were obtained.

**Table 2.** Long-term outcome (frequency and relative risk) with normal and abnormal umbilical artery Doppler ultrasonography

| Outcome | Normal Doppler ($n = 23$) | Abnormal Doppler ($n = 17$) | Relative risk (95% C.I.) |
|---|---|---|---|
| Post-neonatal death | 0 | 1 (6) | – |
| Childhood seizures | 2 (9) | 2 (12) | 1·4 (0·2–8 7) |
| Deaf | 0 | 0 | – |
| Visual handicap | 0 | 0 | – |
| Cerebral palsy | 1 (4) | 1 (6) | 1 4 (0·1–20·1) |
| Squint | 1 (4) | 3 (18) | 4·1 (0·5–35·7) |
| Special school | 1 (4) | 1 (6) | 1·4 (0·1–20·1) |
| Failed DDST | 1 (4) | 1 (6) | 1·4 (0·1–20·1) |
| Height <10th centile | 4 (17) | 5 (29) | 1·7 (0·5–5·4) |
| OFC >2SD below mean | 0 | 1 (6) | – |

DDST = Denver development screening test; OFC = occipito-frontal circumference.
Results are *n* (%) values.

Statistical analysis was by Student's *t*-test, $\chi^2$ test, and calculation of relative risks and 95% confidence intervals (Morris & Gardner 1989).

## Results

Of the 74 pregnancies studied, 34 (46%) had abnormal umbilical artery flow velocity waveforms during the last Doppler study before delivery. Table 1 shows the perinatal outcome.

Of the 40 children reviewed, 17 (43%) had had abnormal umbilical artery flow velocity waveforms at fetal assessment. There were seven reduced, five absent and five reversed diastolic waveform components. Table 2 shows outcome at follow-up. The one death after discharge from hospital and before paediatric review was an infant who died from respiratory failure due to bronchopulmonary dysplasia. One child in each group failed both the Denver developmental screening test and had neurological impairment. In the normal Doppler group, the abnormal child had suffered haemorrhage from the umbilical cord following amniocentesis causing fetal distress, need for emergency caesarean section, and hypoxic-ischaemic encephalopathy. In the abnormal Doppler group, the abnormal child had short stature and dysmorphic features without a specific diagnosis. This child had reduced rather than absent or reversed end disastolic flow.

Table 3 shows perinatal outcome in the 34 fetuses not seen at follow-up. There was no difference between those fetuses and the group as a whole (Table 1). Notes of neonatal unit review until clinic discharge were examined where appropriate. If the infant had not required paediatric review, primary healthy care workers were contacted. Only one child is considered to have possible abnormal development.

**Table 3.** Perinatal outcome with normal and abnormal umbilical artery Doppler ultrasonography in the 34 fetuses not seen at follow-up

| Outcome | Normal Doppler ($n = 17$) | Abnormal Doppler ($n = 17$) |
|---|---|---|
| Intrauterine death | 1 (6) | 2 (12) |
| Neonatal death | 0 | 3 (18) |
| Emergency caesearean section | 3 (18) | 7 (41) |
| Gestational age (weeks) | 36·8 (2·3) | 32·1 (4·2)* |
| Birthweight (g) | 2823 (757) | 1501 (723)* |
| Small-for-gestational age | 3 (18) | 11 (65)* |
| Admitted to neonatal unit | 5 (31) | 13 (87)* |
| Hypoxic-ischaemic encephalopathy | 0 | 0 |
| Respiratory distress syndrome | 1 (6) | 5 (33) |
| Mechanical ventilation | 1 (6) | 5 (33) |
| Intraventricular haemorrhage | 0 | 1 (7) |
| Necrotizing entercolitis | 1 (6) | 2 (13) |
| Neonatal seizures | 0 | 0 |
| Duration of hospital stay (days) | 11·3 (13·0) | 35·1 (32·3)* |

*$P<0·05$.

Results are mean (SD) or $n$ (%) values as appropriate.

## *Comment*

Our aim was to determine whether the established predictive value of Doppler ultrasonography for abnormal outcome extends beyond the perinatal period. Abnormal umbilical artery waveforms reflect pathology in the feto-placental circulation thought to be secondary to structural changes in the tertiary placental villi (Redman 1989). Impaired placental transfer function causes fetal pathology, such as growth retardation, hypoxaemia, and acidaemia. Unfortunately, determination of umbilical artery acid-base status at delivery was not routine at the time of this fetal cohort.

This study supports the positive predictive value of Doppler ultrasonography in high risk fetuses with regard to perinatal outcome. Commonly used indices of adverse perinatal outcome, such as birthweight, gestational age, need for admission to a neonatal unit, and SGA, were all significantly different ($P<0·0001$) in the abnormal Doppler group. However, Neilson (1987) has noted that in many cases, babies are born whilst still very immature, and has suggested that the Doppler investigations are of less prognostic value than the clinical setting.

Doppler ultrasonography did not predict long-term adverse outcome at age 5 years. Table 2 shows very wide 95% CI, showing that the increased risk is not significant. However, the small sample size will also contribute to the wide 95% CI. It is of note that, although not statistically significant, many of the long-term adverse outcomes occurred more often in the group with abnormal Doppler readings. Abnormal Doppler scans gave a relative risk of 1·7 for height below the 10th centile at review. Only one (6%) of the children with an abnormal Doppler study had a head circumference more than 2 SD below the mean at review. We did not present data for weight centiles at follow-up because it is the anthropometric value most affected by current environmental factors. Abnormal Doppler values gave a relative risk of only 1·4 for both cerebral palsy and failure of Denver developmental screening test with very wide 95% CI. In each group, the same child both failed the Denver developmental screening test and had cerebral palsy. This was the child with hypoxic-ischaemic encephalopathy following fetal haemorrhage and the child with the malformation syndrome respectively. Trudinger & Cook (1985) noted that 50% of fetuses with major abnormalities had had abnormal umbilical artery flow velocity waveforms, as in our study. If this child is removed from the analysis, abnormal Doppler ultrasonography becomes even less predictive of abnormal long-term outcome. The Denver developmental screening test was used instead of a more sophisticated test of neurodevelopmental integrity because in this small descriptive study we aimed to elicit major handicap that would have a significant effect on the child's quality of life. We were concerned that 27 children could not be traced or did not attend the follow-up clinic. However, there were no differences in any indices of perinatal outcome between these children and the group as a whole. Further, analysis of existing case notes and discussion with primary health care workers showed only one other child to have been considered to have possible abnormal development. Wariyar & Richmond (1989) noted that difficult-to-trace infants are at high risk of abnormal outcome and this is therefore a drawback in our study.

The poor predictive value of Doppler ultrasonography with regard to long-term outcome as opposed to perinatal outcome is of interest to obstetricians. It would appear that abnormal Doppler scans do not indicate any increased risk of cerebral dysfunction. This is an agreement with a long-term follow-up studies of small for gestational age infants where it was observed that, barring acute perinatal insult, the neurodevelopment of the children was normal (Fitzhardinge & Steven 1972). We acknowledge that the small sample size of this descriptive study means that our results are only a pointer in this important area. A definitive conclusion will require a much larger sample size of high risk fetuses.

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GYNAECOLOGY

# In-vivo studies of uterine electrosurgery

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**ABSTRACT**

**Objective** To study the effects of electrosurgery on the living human uterus.
**Design** Prospective observational study.
**Subjects** Nine women with recurrent refractory dysfunctional uterine bleeding, listed for hysterectomy.
**Intervention** Experimental endometrial resection on patients immediately prior to hysterectomy.
**Main outcome measures** The influence of power output, duration of exposure and repetition of consecutive surgical applications on the size of the zone of thermal necrosis in uterine tissue.
**Results** Resection of the endometrium was associated with a narrow zone of thermal necrosis of between 0·69 and 0·76 mm which was not dependent on power output. Duration of exposure, however, was directly related to tissue necrosis (1·44 *vs* 1·88 mm for 1s and 5s, respectively). Coagulation by pin-point desiccation caused a zone of thermal necrosis of 3·30–3·77 mm that was independent of either power or duration of exposure to electrical energy. Thermal transmission through the uterus *in situ*, during electrosurgery was minimal, the maximum recorded rise in temperature from the baseline was 0·4°C. The differences between the *in vitro* and *in vivo* effects of electrosurgery are highlighted and the possible reasons for these differences explored.
**Conclusions** The potential for unwanted thermally-induced damage to the uterus is small.

Electrosurgical intrauterine ablation, when first reported by DeCherney *et al* (1983), was used in a group of patients who were considered as being too high an operative risk for hysterectomy. These patients, nevertheless, required treatment for intractable uterine bleeding and underwent endometrial ablation using electrosurgery. Since then, a number of alternative methods of endometrial destruction have been described (Magos *et al.* 1989, Vancaillie 1989, Phipps *et al.* 1990 and Goldrath *et al.* 1981). The scope of intrauterine surgery includes the treatment of fibroids, synechiae, and other uterine abnormalities. The method of anaesthesia for intrauterine surgery has undergone changes; sedation and local anaesthetic has recently been reported in 38% of a series of 250 patients (Magos *et al.* 1991).

Intrauterine endosurgery is effective in reducing or stopping menstrual flow, and complications would appear to be few (Magos *et al.* 1991; Vancaillie 1989; Perry *et al.* 1990); perforation, primary haemorrhage, fluid overload and thermally induced damage to adjacent organs are the commonest immediately encountered problems. These complications are thought to be related to operator skill. The skill relies on knowledge of the instruments used, the uterine environment and energy applied, electrical or laser. Awareness of the destructive potential of the equipment used and the uterine anatomical boundaries is important, especially as the role of intrauterine surgery widens and more gynaecologists adopt it into clinical practice.

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The study presented is part of a series designed to assess uterine electrosurgery as an alternative to hysterectomy in women with dysfunctional uterine bleeding refractory to medical treatment. A previous publication by Duffy *et al.* (1991) established the uterine morphometry in this group of women. The important factors relating to tissue destruction and thermal transmission in the *in vitro* model were also identified and quantified. Our study explored these factors in the living model in which uterine blood flow is likely to play an important role in reducing the thermal effect. The influence of power output, duration of exposure, and repetition of consecutive electrosurgical applications on underlying tissue damage and transmitted heat, *in vivo*, was investigated.

## Subjects and methods

Written, informed consent was obtained from each patient, and ethics committee approval was granted for the study.

Patients scheduled for routine hysterectomy, with the diagnosis of dysfunctional uterine bleeding, were approached before surgery and asked to participate in the study. The endometrium was not pre-treated. The patients received a standard anaesthetic and were placed in the modified Lloyd-Davies position on the operating table, thus allowing both abdominal and vaginal surgery. The abdomen was opened and the bowel packed away from the pelvis to enable full view of the uterus, fallopian tubes and ovaries. Transcervical uterine electrosurgery was then performed, under direct vision, using a 27F

Olympus continuous flow hysteroresectoscope (Keymed, Essex, UK). The irrigation solution used was 1·5% glycine at a pressure of 100 mm Hg. After the experimental intrauterine electrosurgery, a routine abdominal hysterectomy was performed and the excised uterus processed as outlined below. The electrosurgical unit was the TD411S (Eschmann Equipment, West Sussex, UK). Both electroresection and electrocoagulation were investigated in terms of tissue effect and thermal transmission through the living uterus.

### *Tissue interaction*

For electroresection a standard 7 mm loop electrode was used. Power output was varied (100, 180 and 260 W blended current) and duration of exposure was increased from 1 to 5s. During the power related experiments in resection, the loop travelled at a speed of 1–1·5 cm/s. Coagulation, using the rollerball, was used in the desiccating mode as described previously (Duffy *et al.* 1991) with the electrode static and in contact with the tissue. Coagulation powers used were 75 and 100 W and the time interval varied from 1 to 5s. Resection was confined to the anterior and posterior walls of the uterus, whilst rollerball desiccation was performed at the cornua and fundus. Following hysterectomy, the uterine specimen was bisected and all insult-bearing tissue excised. These tissue blocks were trimmed and snap frozen in hexane. The blocks were then placed in a cryostat (Slee, London, UK), frozen sections cut and subsequently mounted on glass slides. The sections were incubated to demonstrate the presence or absence of the respiratory enzyme NADH$_2$ diaphorase. The presence of respiratory enzymes within living tissue was indicated by the deposition of formazan which stains a deep purple; formazan was not deposited in dead tissue and therefore remained colourless. For ease of identification the sections were counter stained with nuclear fast red (Nachlas *et al* 1958, Young 1971). The maximum width of the zone of thermal necrosis adjacent to the tissue removed by the resection loop was quantified using a computerized image analysis system (Seescan, Cambridge, UK). Similarly the maximum depth of the zone of thermal necrosis resulting from the desiccating rollerball was also measured (Fig. 1a and b).

### *Thermal transmission*

Because of the incision in the abdomen, continuous temperature recordings of transmyometrial heat dissipation were possible during the intrauterine surgery. The baseline uterine serosal temperature was first established and any changes in temperature resulting from intrauterine electrosurgery were recorded as a rise in degrees centigrade from this baseline. Both a fibreoptic thermometer (Luxtron Biomedical Fluoroptic thermometer, Luxtron Corporation, Mountain View, California, USA) and an infrared thermal camera (Insight Vision, Worcester, UK) were used. The reaction time for the fibreoptic thermometer was 0·3 s with a sensitivity of 0·1°C. Standard thermocouples would not have provided accurate recordings because of interference from the high frequency output of the electrosurgical unit. A chart recorder provided a permanent record of the temperature readings. The reaction time for the thermal camera was quicker (0·03 s), with a sensitivity up to 0·5°C. Video recordings of the thermal images were made for later analysis. Whereas the thermal camera provided a full and rapid picture of the temperature change on the whole serosal surface of the uterus during surgery, the fibreoptic temperature probe could be more precisely placed (on the serosal aspect) in such potential danger areas as the thinner cornua and thus give pin-point information on thermal transmission. Although emphasis was placed on the cornua and isthmus, temperature recordings were also made on the anterior and posterior walls, and fundus of the uterus.

All data were subjected to statistical analysis using Statgraphics Software (STSC, Inc., Rockville, Maryland, USA). The Mann-Whitney *U* test for non-parametric data was used to establish statistical significance. A value of $P < 0{\cdot}05$ was taken as significant.

## Results

Nine women agreed to participate in the study. Ninety-five electrosurgical applications were delivered using both the resection loop and the rollerball. This culminated in 39 blocks of full thickness uterine tissue for histochemical processing and 95 individual temperature recordings.

### *Tissue interaction*

All the data are uncorrected for shrinkage artefact. A correction factor for this of 25% was established in a previous study (Duffy *et al.* 1991) and can be added to the data quoted below. During resection, a zone of thermal necrosis adjacent to the cutting loop of between 0·69 mm and 0·76 mm was produced, with no statistical difference as power was varied (Table 1A). Duration of exposure to electrosurgical cutting energy resulted in a statistically significant increase in the surrounding zone of thermal necrosis (Table 1B). With the rollerball, in the coagulation mode (desiccating output), a consistent zone of thermal necrosis was recorded which did not vary either with power or time increments (Table 1C, D).

### *Thermal transmission*

Ninety-five temperature readings were recorded using both the fibreoptic thermometer ($n = 41$) and the thermal camera ($n = 54$). For simplicity, the energy delivered is expressed in Joules (J) by combining power output and duration of exposure. No measurable temperature change was noted when the pelvis was viewed with the thermal camera, despite alterations in the technique (resection or desiccation), power output, duration of exposure or number of consecutive insults (up to six consecutive insults on four occasions). The range of energies used was from 100-900 J for resection ($n = 22$) and from 100-750 J for coagulation ($n = 32$).

The fibreoptic thermometer recorded a temperature rise (from the baseline) of 0°C to 0·4°C using the resection loop (energy delivered varied from 180 J to 900 J, $n = 19$). The maximum temperature rise (0·4°C) was measured at the fundus when a power of 180 W was delivered for 1s (180 J). For the desiccating output the measured rise in temperature was from 0·1°C to 0.4°C. The latter occurred on the fallopian tube adjacent to the cornua at a power output of 100 W for 5 s (500 J).

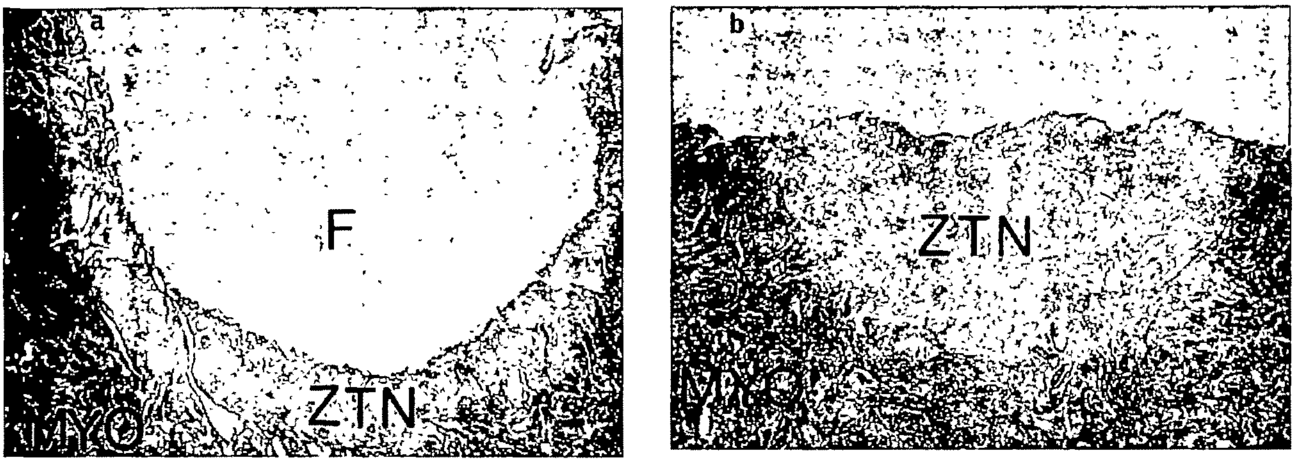

**Fig. 1a.**

**Fig. 1b.**

**Fig. 1.** Photomicrograph of the tissue effect of resection (a) and coagulation (b) on human uterine tissue. The furrow formed by the loop electrode is marked (F). The zone of thermal necrosis (ZTN) is pale in comparison to the darker stained living myometrium (MYO). The narrow band of tissue death adjacent to the lopp (Fig. a) and the semi-circle of underlying tissue necrosis associated with the rollerball (Fig. b), is demonstrated. Incubated to demonstrate NADH$_2$ diaphorase. Reaction product black. Counterstained with nuclear fast red. Original magnification × 10.

The range of energies delivered during desiccation was from 100–500 J.

## Discussion

Although electrosurgery is developing in gynaecology for the treatment of dysfunctional bleeding and intrauterine abnormalities (La Sala *et al.* 1987) very little published work on its tissue effects is available. Safety hinges on how consistent and confined are both the tissue effect and thermal transmission. In a study on gingival resection in dogs *in vivo*, Kelly & Harrison (1975), using older equipment and a partially rectified cutting current, demonstrated a zone of thermal necrosis of between 0·2 mm–0·3 mm, which did not vary with increments of power. In the same study, temperature changes were recorded adjacent to the cutting electrode that varied as power output increased (9°C–16°C at 3 mm from the loop). It must be borne in mind, however, that standard haematoxylin and eosin staining was used to delineate the destroyed tissue. This may not be as accurate in identifying cell death as the histochemical method used in the present study. Also, simple thermocouples were used and these are likely to have made interpretation of the data difficult, as almost certainly the interference from the electrosurgical unit would have prevented simultaneous electrosurgical activation and temperature recording. Nevertheless, the limited tissue destructive potential of electrosurgery was highlighted by this earlier study.

**Table 1.** Zone of thermal necrosis (ZTN) associated with electrosurgery

| Variable | *n* | ZTN (mm) |
|---|---|---|
| A: Resection: Power varied. Resection speed = 1–1.5cm/s | | |
| **Power** | | |
| 100 | 5 | 0·74(0·12) |
| 180 | 10 | 0.76(0·09) |
| 260 | 10 | 0·69(0·2) |
| B: Resection: Power 180 W, time varied | | |
| **Time (s)** | | |
| 1 | 10 | 1 44 (0·29) |
| 5 | 10 | 1·88 (0·30)* |
| C: Desiccation: Time 5s, power varied | | |
| **Power (W)** | | |
| 75 | 5 | 3·30 (1·16) |
| 100 | 5 | 3·77 (0·35) |
| D: Desiccation: Power 100 W, time varied | | |
| **Time(s)** | | |
| 1 | 5 | 3·39 (0·78) |
| 5 | 5 | 3·77 (0·35) |

*P < 0·05

Results are mean (SD) values.

The study reported here investigates electrosurgery in the living human uterus and, for the first time, establishes the basic tissue effects, thermal transmission potential and the relevant contributing factors. Initially it was necessary to investigate the *in vitro* model (Duffy *et al.* 1991) to provide direction for the study of the living model. The *in vitro* data demonstrated that power increments were unrelated to the underlying tissue necrosis in resection and coagulation. Duration of exposure was related to tissue necrosis when using the resection loop and the rollerball in fulgurating mode (spray coagulation). When using the rollerball in desiccation mode (pin-point coagulation), neither power increments nor duration of exposure up to 5s resulted in an increase in tissue necrosis. Coagulation by desiccation produced sufficient tissue necrosis of the deep glands that must be destroyed for adequate treatment, unlike coagulation in the fulguration mode. Thermometry studies, *in vitro*, revealed the importance of power and duration of exposure in thermal transmission during resection. Coagulation using desiccation, on the other hand, was only influenced by time of exposure and not power output. Confirmation of the effects of electrosurgery in the living uterus and investigating the factors, identified as associated with thermally induced damage *in vitro*, was therefore required. The resulting data provide the basis for introduction of a safe technique into clinical practice.

Tissue experiments, as described in this study, indicate that power output, in the living model during resection, does not influence the underlying tissue damage. The zone of thermal necrosis (averaged for all powers) of 0·73 mm (SD 0·15), contrasts with that encountered in our previous *in vitro* study (Duffy *et al.* 1991) where a zone of 1·13 mm (SD 0·55) was recorded (again averaged for all powers). The difference, which is statistically significant, could be due to the cooling effect of uterine blood flow or the effect of the blood milieu on the tissue resistivity, and consequently the voltage delivered by the electrosurgical unit. As in the laboratory based work, duration of exposure to the cutting loop current was positively related to the width of the zone of thermal necrosis (up to 1·88 mm). Coagulation by desiccation, on the other hand, resulted in a similar zone size in both the *in vitro* and *in vivo* settings. The zone of thermal necrosis for desiccation in the living tissue was 3·59 mm (SD 0·76), averaged for all energies delivered, and did not vary with duration of exposure (up to 5s) or power output. Pin-point desiccation would appear to be characterized by the development of a surrounding insulating layer of dried, dead tissue which helped limit further tissue necrosis. The effect may be attributable to the increased resistance found in desiccated tissue which would influence the power output from the generator.

The potential for unwanted thermally induced damage to the uterus and adjacent vital viscera was addressed in this study using both a fibreoptic thermometer and an infrared thermal camera. The fibreoptic thermometer provided accurate and sensitive information on localized areas, such as the cornua. The infrared camera allowed inspection of a larger field within the pelvis, with a quicker reaction time. Neither were prone to interference from the electrosurgical unit. It was clear, with a maximum temperature rise of only 0·4°C on the serosal surface, that the potential for damage, in experienced hands, is small. None of the factors identified *in vitro* appeared to influence the transfer of thermal energy through the uterus in the living model. The likely reason is the very large heat-sink effect of the uterine and pelvic blood flow. It must be stressed that in the narrow confines of the uterus, such as the cornua, extreme caution should be applied.

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# CIN 3: the role of lesion size in invasion

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## ABSTRACT

**Objective** To define the relation between the size of a CIN 3 lesion (measured histologically) and invasive squamous carcinoma.
**Design** Measurement of CIN 3 by computerized planimetry of histological sections from 39 cone biopsies containing microinvasive cancer. Comparison with previous measurements of CIN lesions, associated with different grades of dyskaryosis.
**Results** Microinvasive carcinoma of the cervix is associated with extensive CIN 3 on the surface and in endocervical crypts. The mean size of CIN 3 lesions showing microinvasion is seven times greater than that for severe dyskaryosis without invasion, ($P<0{\cdot}0001$) and a 100-fold greater than with mild dyskaryosis ($P<0{\cdot}00001$).
**Conclusion** Invasive squamous carcinoma of the cervix arises in large CIN 3 lesions and these are associated usually with severe dyskaryosis. We propose a model for the development of high-grade precancer as a small focus within low grade precancer which then undergoes expansion in size, accompanied by apparent progression in cytological grade.

The concept of cervical intraepithelial neoplasia (CIN) aims to unify the morphology of cervical precancer. The range of differentiation is classified into three grades: CIN 1, CIN 2 and CIN 3 (Buckley *et al.* 1982), although the reproducibility and clinical significance of the lower grades are debated (Ismail *et al.* 1989; Robertson *et al.* 1989). The associated cytological changes are graded, in parallel, into mild, moderate and severe dyskaryosis (Evans *et al.* 1986) but it is now accepted that these do not correspond precisely to CIN grades for individual women. Women with severely dyskaryotic smears and whose biopsies contain CIN 3 are at a high risk of developing invasive cancer (McIndoe *et al.* 1984). There are many reports describing cytological progression to invasive cancer, but the complex relation between cytological and histological grades makes it impossible to determine the precise way in which tissue abnormalities progress. Deliberate direct prospective observation of the development of invasive cancer is unethical, and biopsy, inevitably, interferes with the natural history of the disease it attempts to study.

Several studies have shown there is a risk of invasive squamous carcinoma in association with a severely dyskaryotic smear (Singer *et al.* 1984; Souter *et al.* 1986; Lopes *et al.* 1989) of between 1:15 and 1:20. For women with mild dyskaryosis the risk is reduced substantially to between 1:500 and 1:1000 (Jenkins 1991). The management of this risk is debated. Invasive squamous cancer is increasingly detected in young women (Cancer Research Campaign 1990), amongst whom mild dyskaryosis is the most frequent cytological abnormality. Reports of invasive cancer arising directly from CIN 1 are very infrequent, but 20–30% of women with mild dyskaryosis have CIN 3 (Walker *et al.* 1986). Much of the concern over the risk of invasive cancer centres on the importance of this finding. We have shown previously that for women with CIN 3 on cone biopsy, the grade of cervical smear is related to the amount of CIN 3 present (Jarmulowicz *et al.* 1989). CIN 3 lesions found in women with mildly dyskaryotic smears are generally small compared with those associated with moderate or severe dyskaryosis. Many women with mild dyskaryosis have very small CIN 3 lesions, measuring less than 1 mm on a single block of a cone biopsy. Women with severe dyskaryosis often have CIN 3 which involves the whole cervix, including endocervical crypts.

We performed this study to investigate the relation between the size of the CIN 3 component of a precancerous lesion and the presence of microinvasive or subclinical invasive squamous carcinoma of the cervix. Size is of potential importance for understanding both the pathogenesis of invasion in precancer and the relation between smear grade and the risk of invasive disease.

## Subjects and methods

All cone biopsy specimen reports between January 1985 and August 1990 were reviewed, and those containing a small invasive squamous carcinoma were re-examined. Fifty specimens were examined, of which 39 fulfilled the criteria for microinvasive carcinoma as described by Burghardt (1976). Eleven of the 50 specimens were unsuitable for inclusion in the study, either because the tumour had eroded the overlying epithelium, or because of loss of surface epithelium during processing.

Burghardt's criteria are based on volume, as opposed to tumour depth, and the volume of the tumour is determined from three-dimensional measurements. Using these criteria, a microcarcinoma is defined as a tumour with an upper volume limit of 500 $mm^3$.

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Three specimens had depths of invasion exceeding 5 mm, the upper limit of the FIGO definition and were Stage 1a. All cone biopsies received in the laboratory between 1985 and 1990 were cut according to a protocol which required blocking of the entire cervix at the initial cut-up. The method used was identical to that employed previously (Jarmulowicz *et al.* 1989). The cone biopsies examined had all been fixed intact in formal saline for 24 h. They were then bisected and cut into parallel, uniform 2 mm thick blocks, perpendicular to the mucosal surface. A median of 11 blocks were obtained from each cone (range 6–15 blocks), the number of blocks being determined by the size of the cervical os.

The first 4 µm section cut from each block for routine diagnosis and stained with haematoxylin and eosin was used in the study. Diagnosis and grading of CIN were agreed by two pathologists according to the criteria of Buckley *et al.* (1982).

**Table 1.** Total surface length of CIN 3, perimeter length of CIN 3 in glands, and total length of microinvasive component, with maximum depth of microinvasion in 39 cone biopsies

| | Length (mm) | | | |
|---|---|---|---|---|
| Cone | Surface CIN 3 | CIN 3 in glands | Total length of MI | Max. depth of MI |
| 1 | 11·4 | 11 3 | 1·4 | 3·6 |
| 2 | 16·7 | 30·5 | 21·4 | 1·4 |
| 3 | 17·3 | 109·6 | 3·8 | 1·6 |
| 4 | 21·7 | 10·1 | 0·5 | 0·4 |
| 5 | 23·0 | 13·5 | 0·3 | 0·8 |
| 6 | 29·1 | 15·2 | 0 3 | 0·3 |
| 7 | 33·1 | 97 4 | 0·1 | 0·1 |
| 8 | 33·2 | 14·1 | 0·9 | 0·4 |
| 9 | 33·9 | 5·7 | 2·2 | 4·8 |
| 10 | 34·0 | 45·7 | 3·6 | 5·5 |
| 11 | 35·5 | 95·7 | 8·2 | 4·5 |
| 12 | 35·7 | 30 8 | 0·3 | 1·0 |
| 13 | 36·9 | 47 1 | 2·3 | 2·1 |
| 14 | 39·2 | 1·5 | 2·4 | 2·2 |
| 15 | 45·2 | 110·0 | 4·3 | 3 5 |
| 16 | 47·2 | 27·9 | 0·3 | 0·9 |
| 17 | 47·7 | 67·6 | 31·4 | 4·1 |
| 18 | 49·2 | 19·9 | 11·3 | 2·1 |
| 19 | 51·9 | 36·9 | 1·4 | 1·5 |
| 20 | 54·2 | 129·3 | 10·4 | 2·8 |
| 21 | 54·3 | 135·9 | 4·1 | 1 7 |
| 22 | 54·7 | 57·9 | 0 1 | 0·1 |
| 23 | 55·9 | 85 6 | 1·4 | 3·3 |
| 24 | 60·9 | 32·1 | 32·0 | 4·2 |
| 25 | 64·1 | 71·9 | 0·2 | 0 1 |
| 26 | 72·9 | 72·6 | 0·1 | 0·2 |
| 27 | 75·1 | 15·1 | 0·7 | 0·9 |
| 28 | 80 9 | 91·7 | 38·2 | 8·3 |
| 29 | 87·5 | 161·3 | 8·5 | 2·2 |
| 30 | 93·5 | 85·5 | 2·9 | 1·9 |
| 31 | 104·1 | 142·7 | 11 3 | 1·7 |
| 32 | 106·8 | 170 9 | 2·9 | 1·5 |
| 33 | 110·3 | 182·7 | 1·1 | 1·8 |
| 34 | 113·3 | 151·7 | 0·3 | 0 3 |
| 35 | 118·2 | 317·3 | 4·7 | 3·1 |
| 36 | 119·1 | 142·4 | 0·6 | 0·8 |
| 37 | 119·1 | 227·4 | 3·2 | 0·9 |
| 38 | 126·6 | 120·6 | 3·1 | 0·3 |
| 39 | 162·4 | 105·7 | 21·8 | 7·9 |

MI = microinvasive component

A microscope with a camera lucida sidearm was used for measuring. The image was traced onto a digitizing tablet connected to a Kontron MOP videoplan semi-automatic image analyzer.

All measurements were made along the basement membrane. The length of surface CIN 3 was measured in one section from each standard block and then summed. The surface length measured in this way from standard blocks provided a measure of the surface area of CIN 3. The glandular extension was measured by drawing around the basement membrane of involved crypts and summing the perimeter length of CIN 3. The length and maximum depth of any invasive component were also measured.

All measurements were made by one of us (P.T.) and the reproducibility of measurements was confirmed by repeat measurements on five cones picked at random without access to initial results. The repeat measurements of length of CIN 3 and microinvasive carcinoma were consistent to within 5% of the original measurements.

## Results

The results for all 39 cervical cones are shown in Table 1. The total length of CIN 3 on the epithelial surface of the cone biopsies was >20 mm in 36 of 39 (92%), and between 10 mm and 20 mm in the other three cones. There was a positive linear relation between the length of CIN 3 on the surface and the perimeter length of CIN 3 in the underlying glands ($r = 0{\cdot}48$, probability of no slope $<0{\cdot}0001$). There was no correlation between size of the CIN 3 lesion and maximum depth of microinvasion. Table 2 compares these results with the findings in a previous study at our institution (using the same equipment and methods of measurement) which compared the amount of CIN 3 present in cone biopsies from women with two previous abnormal smears of a particular grade of dyskaryosis. The results show that the mean surface length of CIN 3 in those with microinvasion is significantly larger than values seen in mild dyskaryosis (Mann-Whitney $U$ test, $P<0{\cdot}01$).

All 22 cones associated with mildly dyskaryotic smears and 29 of 36 (80%) with moderately or severely dyskaryotic smears contained less than 10 mm of CIN 3 whereas all the

**Table 2.** Comparison of total length of CIN 3 in cone biopsies following abnormal smears with cone biopsies containing microinvasive squamous carcinoma

| | | Length of CIN 3 (mm) | | |
|---|---|---|---|---|
| | *n* | Mean (SD) | (SEM) | Range |
| Previous study* | | | | |
| Smears | | | | |
| Mild | 22 | 0·6 (1 7) | (0·4) | 0 – 7·9 |
| Moderate | 15 | 5·3 (15·7) | (4·1) | 0 – 60·7 |
| Severe | 21 | 9·5 (15·5) | (3·4) | 0 – 53·7 |
| Present study | | | | |
| Microinvasive carcinoma | 39 | 63 5 (37·2) | (6·0) | 11·4–162·4 |

*Jarmulowicz *et al.* (1989).

microinvasive cancers contained more than 10 mm. No cones associated with mild dyskaryosis, and 5 (14%) with moderate or severely dyskaryotic smears had more than 20 mm of CIN 3 compared with 91% of the microinvasive carcinomas (Table 3).

## Discussion

In women with microinvasive carcinoma and an intact measurable precursor lesion, there is usually a very large area of CIN 3 occupying most of the surface of the transformation zone and showing widespread glandular extension. The mean size of CIN 3 lesions associated with microinvasive carcinoma is seven times greater than that for severe dyskaryosis without invasion ($P<0{\cdot}0001$), and a 100-fold greater than with mild dyskaryosis ($P<0{\cdot}00001$). The relatively small number of specimens examined does not allow us to exclude completely the possibility of the occasional development of microinvasive carcinoma from a small CIN 3 or indeed lower grade CIN lesion, but this would not appear to be the usual pathogenesis. The smallest CIN 3 lesion associated with invasion in this study was 11·4 mm in total surface length (about 10–15 $\text{mm}^2$ in surface area).

The 100-fold variation in size, and the association of the risk of microinvasive cancer with large CIN 3 lesions explains many of the apparent discrepancies between progression and cytological and histological gradings of precancer. A pattern of cytological advance from mild dyskaryosis through moderate and severe dyskaryosis to invasive carcinoma has been firmly established. It has been assumed that this change is associated with underlying progression of the affected field of cervical epithelium from CIN 1 to CIN 3 followed by invasive cancer. Such a model has been illustrated in numerous textbooks.

A number of authors (Burghardt 1976; Boonstra *et al.* 1990) have drawn attention to the centripetal structure of CIN with the less differentiated component, CIN 3, being more centrally situated and the well differentiated component, CIN 1, at the periphery. This suggests that high-grade precancer usually begins as a small focus of CIN 2 or 3 situated centrally in the transformation zone, probably in an area of immature squamous metaplasia surrounded by low grade change in more mature metaplastic epithelium. Subsequently, the CIN 3 component expands progressively to replace and, eventually, may obliterate the associated low grade change within the transformation zone. Such expansion would increase progressively the likelihood of moderately or severely dysplastic cells being detected on a cervical smear. Hence, there would be an apparent cytological progression as the CIN 3 lesion expands. Such a model would be consistent with the age distribution of CIN 1, 2 and 3, and with the evidence that larger CIN 3 lesions may occur in older women (Boonstra *et al.* 1990). Expansion associated with increased severity of dysplasia is similar to other precancers such as large bowel polyps. The variation in the risk of invasion with the size of a CIN 3 lesion explains the discrepancy between the high prevalence of CIN 3 in mild dyskaryosis and the relatively low prevalence of invasive cancer. A very small area of CIN 3 does not identify the woman as being at immediate risk of invasive cancer although there may be ultimate progression. Moderate or severe dyskaryosis as a marker for the larger CIN 3 lesion may well be a better guideline for initiating treatment.

Table 3. Relation between cytological grade/microinvasive cancer and total length of CIN 3 present in cone biopsies

| | Length of CIN 3 (mm) | | | |
|---|---|---|---|---|
| | <1 | 1–9·9 | 10–19·9 | >20 |
| Previous study* | | | | |
| Smears | | | | |
| Mild | 20 | 2 | 0 | 0 |
| Moderate | 11 | 2 | 1 | 1 |
| Severe | 11 | 5 | 1 | 4 |
| This study | | | | |
| Microinvasive carcinoma | 0 | 0 | 3 | 36 |

*Jarmulowicz *et al.* (1989).
Results are number of biopsies.

The histological grade and the histological or colposcopic size of a lesion are correlated (Shafi *et al.* 1991). Overall lesion size is potentially important in classifying and managing precancer. Many lesions, however, are complex and some larger lesions may consist mostly of CIN 1 or simple human papilloma virus infection with only a small proportion of CIN 3. The value of the clinical determination of lesion size at cervicography or colposcopy for managing women with mildly abnormal smears needs further investigation.

The development and expansion of a high-grade component within a low-grade lesion is consistent with the multifactorial origin of cervical cancer suggested by both epidemiological and experimental evidence.

Further investigation into lesion size and the mechanism and control of expansion of CIN 3 is likely to yield valuable clinical tools, and to contribute to the understanding of the natural history and histogenesis of cervical cancer.

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GYNAECOLOGY

# The role of partial colpectomy in the management of persistent vaginal neoplasia after primary treatment

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**ABSTRACT**

**Objective** To describe and assess the technique of partial colpectomy for the treatment of persistent vaginal neoplasia.
**Setting** Gynaecological oncology unit of a London teaching hospital.
**Subjects** 12 women with persistent vaginal intraepithelial neoplasia (VAIN) following hysterectomy for cervical intraepithelial neoplasia (CIN) or for benign disease.
**Technique** Partial colpectomy using a vaginal approach assisted by a Schuhardt incision to improve access.
**Results** Assessment of patients between 9 and 99 (mean 55) months after partial colpectomy for VAIN showed no recurrence of disease in ten patients (83%).
**Conclusion** This technique of partial colpectomy is an effective procedure, associated with minimal morbidity which should be considered as primary treatment for patients suffering from persistent vaginal disease after hysterectomy or other procedures.

Malignant tumours of the vagina are rare, occurring at a rate of 0·6 per 100 000 women per year (Cramer & Cutler 1974). While *de novo* vaginal carcinomas may occur, many are preceded by the premalignant changes of vaginal intraepithelial neoplasia (VAIN) (Lenehan *et al.* 1986) often as a result of incompletely excised cervical intraepithelial neoplasia (CIN) at the time of hysterectomy.

VAIN may occur many years after the primary treatment for CIN, so yearly follow-up and vault smears for these patients are essential. As patients are usually asymptomatic and findings on pelvic examination and visual inspection vary (Hernandez-Linares *et al.* 1980), the diagnosis of VAIN is usually made by cytology followed by colposcopically directed biopsy.

Successful treatment of VAIN is difficult and no consensus exists on the most effective treatment. Initial methods of therapy for VAIN were irradiation or surgery, but the complications of potential vaginal shortening and stenosis (Townsend *et al.* 1982; Rutledge 1967) made these treatments less suitable for younger patients and resulted in trials of other treatments. These include topical chemotherapy, immunotherapy and local ablation with diathermy or laser. However, poor long-term success rates and the realization that abnormal epithelium buried beneath the vault suture line was inaccessible to local ablation (Woodman *et al.* 1984) have caused a reappraisal of surgical approaches to this difficult problem.

Traditionally, colpectomy is performed through a midline longitudinal abdominal incision, followed by dissection downwards to the vaginal vault (Monaghan 1986). We report a modified vaginal approach to partial colpectomy which simplifies the procedure and reduces the side-effects for the patient while remaining effective in treating VAIN and other tumours of the vagina.

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## Patients and methods

Twelve women, referred from other centres, attended the gynaecology outpatient clinics of St Bartholomew's Hospital and the Royal Marsden Hospital , London.

The women presented with abnormal cytology during routine follow-up after previous hysterectomy. The indication for previous treatment was CIN III in 11 patients and benign disease in one. Colposcopically directed biopsy confirmed VAIN III in 11 patients and VAIN II in one. Evidence of resection lines being free of residual disease was available in eight patients.

Primary treatment for two of these 12 patients had been irradiation. One of these required vaginoplasty with amnion graft at the time of colpectomy. The remaining 10 had partial colpectomy as primary treatment.

### *Partial colpectomy*

Initial assessment by colposcopy and appropriate cytology and biopsy was performed to delineate the extent of the disease. Schiller's Iodine was applied as a reference marker and was then reapplied in theatre to define iodine-negative areas.

To improve access to the vaginal vault, the vaginal introitus was enlarged by making a Schuhardt incision into the left buttock, using cutting diathermy.

The incision was made at about a 4 o'clock position, passing through skin and sub-cutaneous tissues. Deep to this, the transverse perineii muscles were incised, and the incision was extended midway up the vagina until the fascia covering the levator ani was exposed on the left side. By carefully displacing the rectum inferiorly, and the levator ani laterally, access was improved.

The upper third of the vagina, or more if clinically indicated, was incised circumferentially with cutting diathermy. By sharp dissection initially, to define a plane beneath the vaginal epithelium, the recto-vaginal space was developed and the rectum stripped digitally from the vagina posteriorly. Similarly, dissecting anteriorly, the bladder was mobilized and retracted superiorly.

The ureters were then palpated at the vaginal angles and digitally 'rolled' in a supero-lateral direction as the bladder was mobilized to ensure that they were adequately displaced from the vaginal epithelium which was to be removed.

The vaginal vault was then grasped with 'Allis' forceps or by inserting several interrupted sutures to provide descent with traction. Dissection may be facilitated by insertion of a small gauze swab, with closure of the incised vagina around it. This provides more substance to dissect on and allows more traction.

By both sharp and blunt dissection, the vaginal epithelium to be retained was pushed back distally towards the introitus. The vault was then excised allowing an adequate cuff of vagina to ensure the margins of resection were clear of the colposcopically identified atypical transformation zone. The specimen was marked with a suture to facilitate histological examination. The excision lines of the specimen were sampled for immediate frozen section to confirm adequate resection margins.

As peritoneum is not normally opened, the 'new' vaginal vault could be closed with interrupted catgut sutures. A vacuum drain was left for 48 h to drain the rectovaginal space superiorly, and the Schuhardt incision inferiorly. The drain was brought out posteriorly in the buttock at the apex of the incision. The prerectal fascia was then repaired, followed by the vagina and skin of the buttock, all with absorbable interrupted sutures, as for a large episiotomy. Colpoperineorrhaphy was performed if required. A vaginal pack and urethral catheter were inserted for 48 h.

## Results

The mean age of the women presenting with VAIN was 50 years (range 33–63). The mean interval after primary treatment to the development of abnormal cytology was 28 months (range 3–120). A vaginal cuff had been taken at the time of hysterectomy in 8 of the 12 women presenting with VAIN III.

Pre-operative colposcopy demonstrated lesions involving the vaginal angles in nine patients. Despite colposcopic identification of the lesions and despite frozen section, the resection margins of the histology specimen were not clear of disease in two patients. In the remaining 10 patients the margins were clear.

The operative procedure was well tolerated by all the patients and the mean post-operative stay was eight days (range 3–14). There were no immediate complications, apart from post-operative pyrexia in one patient. One patient complained of dyspareunia, vaginal shortening and stress incontinence and required vaginoplasty 20 months later. There was no other long-term morbidity related to the procedure.

At the time of writing the mean duration of follow-up is 55 months (range 9–99). Ten women (83%) are alive with no sign of recurrent disease.

The two patients with residual disease within the resection margins have required further therapy. The first has been treated with carbon dioxide laser on two occasions for recurrent VAIN III and continues to be closely reviewed.

The second patient had already been treated with diathermy for persistent VAIN III, 2 months after hysterectomy for CIN III. Cytology remained abnormal and colposcopically directed biopsies showed invasive carcinoma. She was treated with radiotherapy but abnormal cytology persisted and after 2 years VAIN III was found on biopsy. Colpectomy with amnion graft vaginoplasty was performed. Three years later, she developed invasive carcinoma within the amnion graft site and required pelvic exenteration. Two years following exenteration she has no further signs of recurrent disease.

## Discussion

The possibility of recurrent vaginal disease after primary treatment for cervical lesions has been recognized for many years (Graham & Meigs, 1952), and can occur up to 24 years later (Petrilli *et al.* 1980). While most of these cases have histological evidence of non-invasive disease, it is well established that the natural history is progression to invasive carcinoma of the vagina (Gallup & Morley 1975).

Attempts at conservative treatment of the disease with electrocautery, carbon dioxide laser, 5-fluorouracil or 2-4-dinitrochlorobenzene have been reported over the last decade. Whereas the initial results seemed to be encouraging, the follow-up period was limited or not specified (Petrilli *et al.* 1980; Townsend *et al.* 1982). More recent reports have been less impressive, with a 57% failure rate 30 months (mean) after laser treatment in one study (Woodman *et al.* 1984). Furthermore, the development of invasive disease after local treatment with electrocautery, local excision and laser (Woodman *et al.* 1984; Lenehan *et al.* 1986) and the unexpected finding of invasive disease in surgically resected specimens (Ireland & Monaghan, 1988) has led to the suggestion that these forms of treatment should not be used for residual vaginal disease after hysterectomy (Soutter 1988).

Surgery has been advocated as the treatment of choice. It is more effective after long-term follow-up (Lenehan *et al.* 1986) and allows further histologic examination. This is especially important when initial treatment was for invasive disease and can assess whether resection is complete. The potential disadvantages are vaginal shortening and stenosis, and the difficulty and morbidity associated with the procedure when it is performed abdominally. These problems can be reduced by a vaginal approach which allows less dissection and removal of the minimum amount of vagina required. Reported difficulties of clamping the vaginal arteries at the vault angles (Soutter 1988) are eased by the use of the Schuhardt incision to improve access. Early post-operative use of vaginal dilators and topical oestrogen cream are beneficial in reducing coital difficulties, the remaining vagina usually stretching as necessary.

Irradiation is also effective in eradicating disease with low long-term recurrence rates (Woodman *et al.* 1988). However, it is associated with significant morbidity. The risk of vaginal adhesions, shortening and stenosis make it less acceptable for use in younger patients. Furthermore it carries an appreciable risk of premature ovarian failure (Woodman *et al.* 1988) and a theoretical risk of subsequent radiation induced pelvic malignancy.

The percentage of women with recurrent disease after colpectomy for VAIN III was 17%. This may have been reduced if the resection margins had been clear of disease in all cases. Incomplete excision occurred despite pre-operative colposcopy and frozen section analysis. This may have been the result of multiple microscopic foci of intraepithelial disease, unfortunately missed by the frozen section sampling, but which may have remained even if the lines of resection had appeared to be clear. If so, these would also have been unknowingly missed by local ablative therapy but not by radiotherapy.

Irrespective of whether residual disease remains, it is imperative to follow-up patients post-operatively, initially with colposcopy and cytology until confirmed clear of disease. Subsequently, annual cytological examination should be continued indefinitely.

We have also used this procedure for other vaginal lesions including: vault recurrence of an endometrial carcinoma; CIN III within a cervical stump after sub-total hysterectomy; incomplete excision at hysterectomy of Stage 1a occult carcinoma of the cervix; vaginal leiomyosarcoma; and vaginal adenocarcinoma following Wertheim's hysterectomy for adenocarcinoma of the cervix. All except the latter case have remained disease free without further treatment after a follow-up interval of 18 to 58 (mean 34) months. This latter patient has required radiotherapy on two occasions and is currently free of disease.

The morbidity associated with this procedure is low. Partial colpectomy performed in this way is a relatively simple and effective procedure which should be considered as treatment for young sexually active patients with recurrent vaginal disease after hysterectomy or other procedures.

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GYNAECOLOGY

# Leiomyosarcomas have a poorer prognosis than mixed mesodermal tumours when adjusting for known prognostic factors: the result of a retrospective study of 423 cases of uterine sarcoma

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## ABSTRACT

**Objective** To determine the survival data for the various tumour types of uterine sarcoma and determine the influence of various prognostic factors on survival.
**Design** Retrospective analysis of all uterine sarcoma cases registered in the 15 year period 1967–1981.
**Setting** West Midlands Regional Cancer Registry, serving a catchment area of 2·6 million women.
**Subjects** 423 women registered as having a uterine sarcoma; 367 of these were associated with the two main histological types, leiomyosarcomas (LMS) and mixed mesodermal tumours (MMT).
**Main outcome measures** Duration of survival was taken as the primary endpoint.
**Results** The overall 5-year survival for uterine sarcomas in this series was 31%, with the major prognostic indicator being tumour stage. Survival for mixed mesodermal tumours is similar to other sarcomas despite a tendency towards less differentiation, wider dissemination and a greater age of the patient at diagnosis. Multivariate analysis shows that for cases with similar stage, age and grade, mixed mesodermal tumours have a better prognosis than leiomyosarcomas.
**Conclusions** These results demonstrate the danger of considering each variable in isolation when the relation between variables can lead to spurious significance or lack of significance because of the imbalances in the numbers between groups of prognostic importance. This study underlines the need for an adequate inspection of the intra-abdominal contents at the time of hysterectomy for uterine fibroids.

Uterine sarcoma accounts for only 1–3% of all female genital tract malignancy (Salazar & Dunne 1980; Sengupta & Sparke 1981) and between 3–7% malignant tumours of the corpus uteri (Salazar & Dunne 1980; Cavanagh *et al.* 1979). To provide more information for clinicians involved in the management of women with uterine sarcoma, a retrospective study was undertaken using cases reported to the Birmingham Regional Cancer Registry during the 15 year period 1967–1981. It was hoped that such an analysis would yield survival data for the various tumour types, and provide useful information with regard to the prognostic factors of this rare gynaecological malignancy.

## Patients and methods

Data were collected from the records held at the West Midlands Cancer Registry of women with uterine sarcoma registered in the 15 year period 1967–1981, and transcribed onto a dual VAX 3600 minicomputer at the CRC Trials Unit, Birmingham. This regional cancer registry serves a female catchment population of 2582 million (1971 population census). It is considered that the West Midlands region contains proportions of industrial, commercial and agricultural subpopulations similar to those found nationally (Waterhouse 1974). Efficiency of case registration exceeds 95% and less than 1% registered cases are untraced.

In all but 24 of the 423 cases presented, a 5-year follow up has been achieved (i.e., a >94% 5-year follow-up). Data were taken mainly from registry records but where information was lacking further details were sought from case notes. Written consent was obtained from the appropriate clinicians in the region.

The statistical analyses were performed using the 'BMDP' statistical software (Dixon *et al.* 1990). Exploratory data

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**Table 1.** Population characteristics ($n$ = 423)

| Group | $n$ | (%) |
|---|---|---|
| Histological type | | |
| Leiomyosarcoma | 215 | (51) |
| Mixed mesodermal tumour | 152 | (36) |
| Endometrial stromal sarcoma | 26 | (6) |
| Other | 30 | (7) |
| Stage | | |
| I | 253 | (60) |
| II | 23 | (6) |
| III | 77 | (18) |
| IV | 67 | (16) |
| NK | 3 | |
| Menopausal status | | |
| Premenopausal | 116 | (28) |
| Postmenopausal | 305 | (72) |
| NK | 2 | |
| Differentiation | | |
| Well | 136 | (37) |
| Moderate | 136 | (37) |
| Poor | 100 | (26) |
| NK | 51 | |
| Surgery | | |
| Biopsy only | 51 | (12) |
| No residual | 317 | (76) |
| Residual | 50 | (12) |
| NK | 5 | |
| Chemotherapy | | |
| None | 360 | (86) |
| Palliative | 49 | (12) |
| Adjuvant | 9 | (2) |
| NK | 5 | |
| Radiotherapy | | |
| None | 290 | (69) |
| Palliative | 55 | (13) |
| Adjuvant | 73 | (18) |
| NK | 5 | |

NK = unknowns.
Median age = 60 years, range (24–95) years.
Median age of menopause, 50 years.

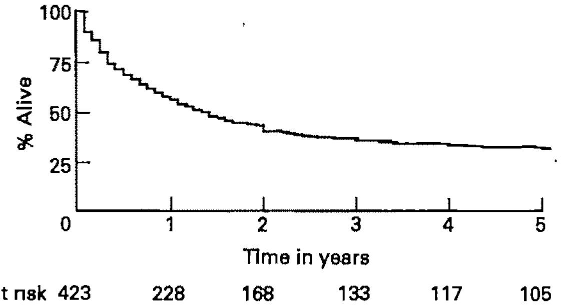


**Fig. 1.** Overall 5-year survival of 423 women with uterine sarcoma.

analysis used Pearsons $\chi^2$ statistic and the Mann–Whitney nonparametric test to determine associations inherent in the data. For the analysis of this report the duration of survival was the primary endpoint. Survival was determined as the time from diagnosis until the date of death. Women who died of causes other than cancer were censored at their date of death. Initial univariate analysis of potential prognostic factors associated with survival was performed using Kaplan-Meier survival curves and the Log-rank test (Peto *et al.* 1977). The independence of these factors was tested using the Cox stepwise regression analysis (Cox 1972).

## Results

### *Population characteristics*

In the 15-year period 1967–1981, 423 cases of uterine sarcoma were registered, giving an annual incidence of 1.64/100 000 female population. Leiomyosarcomas accounted for 51% (215 cases), mixed mesodermal tumours 36% (152 cases) and endometrial stromal sarcoma 6% (26 cases). Other rarer histological types have been grouped together with those of indeterminate histology 7% (30 cases). The histological distribution is similar to that described for other series of uterine sarcoma (Piver & Lurain 1981). During the first 10 years of the period analysed, there were 11 cases of adenocarcinoma registered for every case of uterine sarcoma (Oláh *et al* 1991).

The population characteristics of the total 423 cases presented are shown in Table 1. The age range at presentation was from 24–95 years with a mean of 60 years. Exactly 90% were aged 45 or over, and over 70% of women were post-menopausal. The age distribution in this study was similar to those described previously (Salazar *et al.* 1978*a*; Vardi & Trovell 1980; Mantravadi *et al.* 1981). Age was highly associated with histological type, the leiomyosarcomas tending to present in younger women ($\chi^2 = 50{\cdot}6$, d.f. = 6, $P<0{\cdot}0001$). A bimodal distribution is demonstrable and is thought to be a reflection of the later mean age at which mixed mesodermal tumours present (Taylor 1972; Oláh *et al.* 1991). A larger proportion of mixed mesodermal tumours were found in post menopausal women (mixed mesodermal tumours 91%, leiomyosarcomas 58%), and there were proportionately more leiomyosarcomas in the premenopausal group (mixed mesodermal tumours 9%, leiomyosarcomas 42%). This association was highly significant ($\chi^2 = 45{\cdot}9$, $P<0{\cdot}0001$).

It has been shown that mixed mesodermal tumours tend to present with more advanced disease than either leiomyosarcomas or endometrial stromal sarcomas. In addition, older women, in whom mixed mesodermal tumours are more common, tend to present with more widespread disease (Salazar & Dunne 1980; Salazar *et al* 1978*a*, 1978*b*).

### *Univariate analysis*

The survival analysis is based on the total 423 cases registered over the 15-year period. At the time of the analysis, 124 (29%) remained alive; the median follow-up time for these cases was 8 years with 94% followed-up for at least 5 years. Only 19 (5%) of the 423 cases did not die of their disease and were censored as at their date of death. The overall median survival time is 16 months (95% CI 13 to 19 months) and the 5-year survival is 31% (95% CI 26% to 36%). The survival distribution is shown in Fig. 1. Univariate log-rank analysis identified factors significantly associated with survival (Table 2). Variables considered included age, histological type and grade, stage, menopausal status and treatment. All these factors were significantly associated with survival, with the exception of histological type ($P$ = 0·45), see Fig. 2.

Table 2. Univariate log-rank survival analysis ($n = 423$)

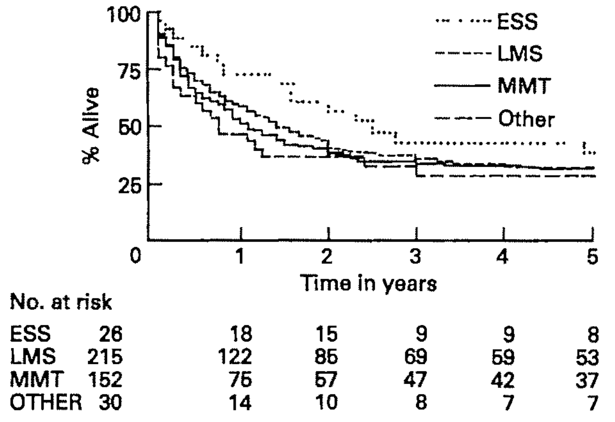
| Group | Number dead | % Alive | Median survival (months) | DF | $\chi^2$ | *P*-value | Survival improved in |
|---|---|---|---|---|---|---|---|
| Histological type | | | | | | | |
| LMS | 142/215 | 34 | 17 | 3 | 2·66 | 0·45 | ESS |
| MMT | 102/152 | 33 | 13 | | | | |
| ESS | 15/26 | 42 | 30 | | | | |
| Other | 21/30 | 30 | 9 | | | | |
| Stage | | | | | | | |
| I | 123/253 | 51 | 52 | 3 | 221·75 | <0·0001 | Stage I, II |
| II | 20/23 | 13 | 16 | | | | |
| III | 69/77 | 10 | 5 | | | | |
| IV | 65/67 | 3 | 3 | | | | |
| Age (years) | | | | | | | |
| <50 | 37/87 | 57 | nr | 1 | 32·22 | <0·0001 | Younger |
| >50 | 243/336 | 28 | 12 | | | | |
| Menopausal status | | | | | | | |
| Pre- | 52/116 | 55 | nr | 1 | 41·88 | <0·0001 | Pre-menopausal |
| Post | 227/305 | 26 | 10 | | | | |
| Differentiation | | | | | | | |
| Well | 56/136 | 59 | nr | 2 | 92·63 | <0·0001 | Well |
| Moderate | 98/136 | 28 | 14 | | | | |
| Poor | 90/100 | 10 | 6 | | | | |
| Surgery | | | | | | | |
| No residual | 182/317 | 43 | 27 | 2 | 163·50 | <0·0001 | No residual |
| Residual | 44/50 | 12 | 5 | | | | |
| BX-only | 50/51 | 2 | 3 | | | | |
| Chemotherapy | | | | | | | |
| None | 220/360 | 38 | 17 | 2 | 10·55 | 0·005 | No treatment |
| Palliative | 47/49 | 4 | 14 | | | | |
| Adjuvant | 9/9 | 0 | 22 | | | | |
| Radiotherapy | | | | | | | |
| None | 173/290 | 40 | 18 | 2 | 11·39 | 0·003 | No treatment |
| Palliative | 50/55 | 9 | 13 | | | | |
| Adjuvant | 53/73 | 27 | 18 | | | | |

Abbreviations: LMS = leiomyosarcoma, MMT = Mixed mesodermal tumour, ESS = endometrial stromal sarcoma; nr = not reached

*Multivariate analysis*

To determine the independent prognostic effect of each of the factors and to exclude the possibility that the most highly significant variables might be masking the effect of other potentially significant factors, a multivariate analysis based on the Cox proportional hazards model (Cox 1972) was performed. All of the variables considered in the univariate analysis were used and a stepwise procedure was adopted. Only cases for the two main histological types, leiomyosarcomas and mixed mesodermal tumours were considered ($n = 367$). The criteria for inclusion of a variable was $P<0{\cdot}05$ and for exclusion $P>0{\cdot}05$. For the Cox multiple regression only cases with complete data for all variables are included in the development of the model and thus, to increase the number of cases considered, the analysis was repeated using only the variables that entered the final model. Differentiation is an important variable, but 39 out of the 367 cases were ungraded. Including these ungraded cases in a group of their own in the univariate log-rank analysis for grade showed that they cannot be thought to be missing due to poor grading, as these unknown cases had a better survival than the moderately graded cases. Consequently these 39 cases were excluded. Thus, the multivariate analysis was based on the remaining 328 cases.

The proportionality assumptions of the method were tested graphically using stratified Cox's regression analysis and looking at the log minus log survival function plots. The stability of the variables entered into the final model was examined by repeating the analysis excluding each variable in turn. This



| No. at risk | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| ESS | 26 | 18 | 15 | 9 | 9 | 8 |
| LMS | 215 | 122 | 86 | 69 | 59 | 53 |
| MMT | 152 | 76 | 57 | 47 | 42 | 37 |
| OTHER | 30 | 14 | 10 | 8 | 7 | 7 |

Fig. 2. 5-year survival by histological type: ESS = endometrial stromal sarcoma; LMS = leiomyosarcoma; MMT = mixed mesodermal tumour ($P = 0{\cdot}45$).

**Table 3.** Summary of the Cox multiple regression analysis for tumour types leiomyosarcoma (LMS) and mixed mesodermal tumour (MMT) ($n = 328$)

| Step no. | Group | | Regression coefficient ($\beta$) | $\chi^2$-to remove | $P$-value | Risk ratio* (95% CI) |
|---|---|---|---|---|---|---|
| 1 | Stage | I, II, III, IV | 0·5291 | 70·55 | <0·0001 | 4·89 (4·08–5·87) |
| 2 | Differentiation | Well, Mod, Poor | 0·5517 | 31·11 | <0·0001 | 3·02 (2·48–3·67) |
| 3 | Age | Continuous | 0·0297 | 31·29 | <0·0001 | 1·81 (1·59–2·06) |
| 4 | Histological type | MMT, LMS | −0·1853 | 6·14 | 0·013 | 1·45 (1·25–1·68) |

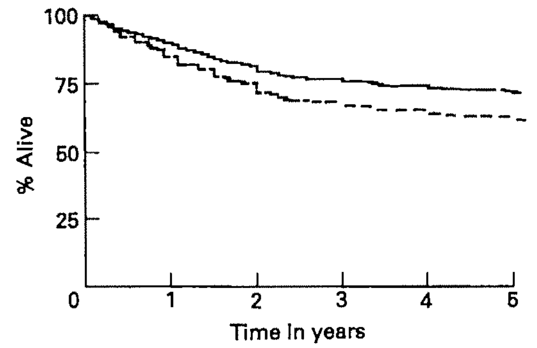
*The risk ratios are calculated from the formula $[\exp(\beta)]^k$, where k = the difference between the high risk (stage IV, differentiation poor, age 70, histological type LMS) and low risk (stage I, differentiation well, age 50, histological type MMT) groups; e.g., for age k = 20 when comparing the risks of a 50-year-old with a 70-year-old woman.

was performed to identify any inherent associations in the data. The adjusted hazard ratios, together with their 95% CI, were calculated using the regression coefficient from the final model. Table 3 summarizes the results from the final model identifying stage, age, grade and tumour type as independent variables. The results of this analysis show a significant effect of histology on prognosis ($\chi^2$ to remove = 6·14, $P$ = 0·013) with leiomyosarcomas having a poorer survival than mixed mesodermal tumours, risk ratio of 1·45. The final model was used to predict the 5-year survival distribution for a stage 1, well differentiated, age 50 woman by tumour type. The predicted 5-year survival for leiomyosarcoma was 61% and 72% for mixed mesodermal tumour for this set of covariates, (see Fig. 3), emphasizing the worse prognosis of leiomyosarcoma on survival when accounting for the three main prognostic factors of stage, age and grade. This is in contrast to previous reports (Salazar *et al.* 1978*b*; Aaro *et al.* 1966; Badib *et al.* 1969) and to our own findings in the univariate analysis.

## Conclusion

The overall 5-year survival in this series was 31% (95% CI 26% to 36%). As in other gynaecological malignancies, tumour stage was the main prognostic indicator (Table 3). Not only did the spread of the tumour affect the prognosis, but in addition, as in previous studies (Kempson & Bari 1970) the size of the primary tumour influenced patient survival.

Increasing age was closely associated with decreased survival, and postmenopausal women had a poorer prognosis, even when the data were corrected for age (Vardi & Trovell 1980). No difference in survival was found between the main histological variants of uterine sarcoma when a univariate analysis was performed. Thus, overall survival for mixed mesodermal tumours is similar to that of other sarcomas despite a tendency towards less differentiation, wider dissemination at the time of diagnosis and a greater age of the patient, the vast majority of whom are post-menopausal. However, multivariate analysis shows that if like cases for stage, age and grade are compared then mixed mesodermal tumours carry a better prognosis than leiomyosarcomas. These results demonstrate very well the danger of considering each variable in isolation when the relation between the variables can lead to spurious significance or lack of significance because of the imbalances in the numbers between groups of prognostic importance.



| No. at risk | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| LMS | 198 | 117 | 80 | 66 | 57 | 51 |
| MMT | 130 | 66 | 50 | 40 | 36 | 32 |

**Fig. 3.** Predicted 5-year survival by tumour type for a woman aged 50 with stage 1, well differentiated tumour ($n$= 328) (——) mixed mesodermal tumour (MMT); (---) leiomyosarcoma (LMS).

It has been shown that 35–37% stage I-II sarcomas have positive pelvic lymph nodes, with 14·3% having aortic lymph node involvement (Piver & Lurain 1981). In some series as many as 45% of stage I sarcomas had lymph node metastases to both pelvic and para-aortic nodes (Chen 1989). This high rate of nodal involvement was associated with deep myometrial invasion, uteri with a cavity of more than 8 cm in length, patients older than 65 years and leiomyosarcoma tumours (Chen 1989). The association with leiomyosarcomas is important in the context of our findings, and suggests a mechanism by which early spread can occur, thus influencing the overall survival for this tumour. An adequate inspection of the intra-abdominal contents at the time of hysterectomy for uterine fibroids should be performed. Suspicious clinical features such as rapid growth or pain should alert the clinician to the possibility of uterine sarcoma.

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CLINICAL PRACTICE

# Ruptured splenic artery aneurysm in pregnancy. A review

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Rupture of any arterial aneurysm is a rare event in young women. Half of all arterial aneurysm ruptures in women of child bearing age occur during pregnancy (Barret *et al.* 1982) and this diagnosis should always be considered in any pregnant patient who has unexplained hypotension and abdominal pain.

The splenic artery is the third most common site of intra-abdominal aneurysm formation after the abdominal aorta and the iliac vessels. Splenic artery aneurysms are unusual because they occur more frequently in women and they are seen at a relatively younger age than aneurysms of the great vessels. They are associated with increasing parity and have a particular tendency to rupture in pregnancy. Rupture of these aneurysms carries a high maternal and fetal mortality and only with prompt treatment can this high mortality be reduced.

## Historical background

A splenic artery aneurysm was first described in 1776 by Beussier (Lie *et al.* 1990) and rupture in pregnancy in 1869 by Corson (Ho 1977). In 1889 President Garfield died from a ruptured splenic artery aneurysm which was traumatic in origin following a bullet wound (Moore & Lewis 1961). An aneurysm was first described in a living person in 1903 by Winkler when several small dilatations of the splenic artery were found at operation (Lie *et al.* 1990). In 1920, the first pre-operative diagnosis was made by Höegler who heard a murmur over a pulsatile mass investigated by fluoroscopy and, in 1930, the phenomenon of a double rupture was described by Brockman (Lie *et al.* 1990). In 1932, the first pre-operative diagnosis followed by a successful operation was made by Lindboe (Lie *et al.* 1990). The first maternal survivor following rupture in pregnancy was not described until 1940 by MacLeod and the first report of both fetal and maternal survival was in 1967 (Vassalotti & Schaller 1967).

## Incidence and occurrence

The overall prevalence of splenic artery aneurysms is unknown. They are found in approximately 0·07% of routine post-mortems; however, the incidence at post-mortem in those over 60 years of age is as high as 10·4%. Overall 79% of splenic artery aneurysms occur in people over 50 years of age. A high prevalence has been reported in some angiographic series ranging from 0·78–7·1%, but these are in selected patients with known arteriopathic disease (Moore & Lewis 1961; Stanley & Fry 1974; De Vries *et al.* 1982; Trastek *et al.* 1985; Williams 1988).

In contrast to aneurysms of the great vessels, which are more frequent in men, splenic artery aneurysms are 2–5 times more common in women and tend to occur at a younger age (Stanley & Fry 1974; Lie *et al.* 1990; Trastek *et al.* 1985; Williams 1988). The two principal factors that are of importance in the development of these aneurysms are grandmultiparity and portal hypertension. About 25% of women with a splenic artery aneurysm have been pregnant more than six times. In one report 87% of the aneurysms were found in women and 92% of them had had between 1 and 16 pregnancies, the mean number of pregnancies being 4·5 (Trastek *et al.* 1982). Aneurysms have also been described in the first pregnancy although this is unusual (Trastek *et al.* 1985; Williams 1988).

Up to 24% of splenic artery aneurysms are found in patients with portal hypertension (De Vries *et al.* 1982; Pomerantz *et al.* 1986; Lowry *et al.* 1986) and the incidence is said to be 7·1% in cirrhotics (Stanley & Fry 1974). Aneurysms have been found in 8·4% of patients having routine coeliac angiography prior to liver transplantation (Ayalon *et al* 1988).

## Complications

Over 80% of splenic artery aneurysms are asymptomatic and are discovered incidentally at angiography, laparotomy or post-mortem (Trastek *et al.* 1985). The principal complication of a splenic artery aneurysm is rupture. This can lead to either a sudden onset of hypovolaemic shock if rupture is into the peritoneal cavity or it may lead to a more insidious anaemia associated with rupture into the gastrointestinal tract. Rupture into the stomach, small bowel, colon and pancreatic duct have all been reported and gastro-intestinal bleeding is a presentation in one third of cases (Lie *et al.* 1990; Bishop 1984; De Vries *et al.* 1982).

Overall, rupture of a splenic artery aneurysm is an uncommon event and is reported in 2–9% of cases. However, between 20% and 50% of ruptures occur in pregnancy and another 20% occur in patients with portal hypertension (Stanley & Fry 1974; Barrett *et al.* 1982; De Vries *et al.* 1982; Trastek *et al.* 1985).

Rupture is said to be unlikely in aneurysms smaller than

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2·5 cm although it has been reported in lesions of 1–2 cm in size (Trastek *et al.* 1985; De Vries *et al.* 1982; Salo *et al.* 1986). The mortality from rupture was historically very high but this has been reduced due to advances in surgery and resuscitation. The mortality from rupture is now approximately 10% rising to 25% when there is free rupture into the peritoneum. (Trastek *et al.* 1985; Mehrota *et al.* 1983; De Vries *et al.* 1982; Bishop 1984).

## Rupture in pregnancy

Up to one half of all ruptured splenic artery aneurysms occur in pregnancy; 69% rupture in the third trimester, 12% in the first two trimesters, 13% in labour and 6% in the puerperium (Barrett *et al* 1982). Although gastrointestinal bleeding is a presentation in one third of all ruptures, this is never a feature of rupture in pregnancy which is always into the peritoneal cavity (Lowry *et al* 1986; Walker *et al.* 1988).

The maternal mortality from rupture in pregnancy is 71% and fetal mortality is as high as 95% (Trastek *et al.* 1985; Mehrota *et al.* 1983; De Vries *et al.* 1982; Bishop 1984). Only nine instances of both maternal and fetal survival have been reported (Vassalotti & Schaller 1967; Mehrota *et al.* 1983; Lowry *et al.* 1986; Donovitz *e al.* 1986; Salo *et al.* 1986).

## Clinical features

Splenic artery aneurysms usually remain undetected unless they rupture (Lie *et al.* 1990). Large aneurysms may give rise to pain (Jones & Finney 1968) and in one series, chronic non-specific abdominal pain, usually in the left hypochondrium, occurred in 13% and bruits were audible in 11% (Trastek *et al.* 1982).

When aneurysms rupture there is a sudden onset of severe abdominal pain associated with hypotension. The pain is usually felt in the epigastrium, penetrating to the back, or radiating to the shoulder tip (Moore & Lewis 1961). The pain is often associated with nausea and vomiting. If the aneurysm has ruptured into the gastrointestinal tract both haematemesis and melaena may occur. Occasionally aneurysms can give rise to a chronic iron-deficiency anaemia (Lie *et al.* 1990).

Tenderness in the upper abdomen is often the only clinical sign. This can vary in severity from mild tenderness with guarding, to a picture of generalized peritonitis. There can be a palpable abdominal mass but this may be confused with the spleen in patients with portal hypertension. In pregnant women the tenderness can be diffuse or maximal over the fundus of the uterus (Williams 1988).

The phenomenon of a 'double rupture' is reported in 20% of patients. The patient presents with a sudden onset of abdominal pain and hypotension which recovers rapidly with simple fluid replacement. There is then a latent period followed by a sudden cardiovascular collapse, usually within 48 h. This picture results from a small premonitory bleed into the lesser sac which becomes contained and is followed by free rupture into the peritoneum (De Vries *et al.* 1982; Lie *et al.* 1990; Lowry *et al.* 1986).

## Pathological features

Aneurysms have been described from 1 to 30 cm in diameter but they are usually 2–3 cm in size; 78% are located in the distal one third of the vessel and are saccular in nature (Trastek *et al.* 1985).

The aetiology of these aneurysms remains uncertain. Although arterio-sclerosis is reported in 95% of lesions and calcification in 70%, these are believed to be secondary changes resulting from increased turbulance rather than the primary causative factors Fibromuscular arterial dysplasia is described in 4–30% of patients. Mycotic aneurysms of the splenic artery are very rare and only account for 2% of all mycotic aneurysms (Moore & Lewis 1961; Stanley & Fry 1974; De Vries *et al.* 1982; Trastek *et al.* 1985).

### *Pathogenesis of splenic artery aneurysms*

An increased splanchnic blood flow is seen in both portal-hypertension and pregnancy and the increased splenic artery blood flow is probably the principal factor in the development of aneurysms at this site.

In portal hypertension, an increased portal inflow pressure is required to maintain portal perfusion. This is achieved by an increased splanchnic arterial flow through both the splenic and superior mesenteric arteries (Sato *et al.* 1987; Nishida *et al.* 1986). Physiological changes induced by pregnancy include an increased blood volume and cardiac output, relative portal congestion and systemic hypertension. Ohlson (1978) also demonstrated that the pregnant uterus causes significant occlusion of the aorta and the iliac vessels during the third trimester which results in an increased blood flow through arteries more proximal to the site of compression including the splanchnic vessels.

It is believed that the combined effects of increased flow and altered arterial structure places a greater stress on the vessel. Individuals who have underlying arterial disease are more susceptable to these stresses leading to aneurysm formation.

In pregnancy, hormonal changes can affect the structure of the arterial wall leading to disruption of the internal elastic lamina and failure of elastin formation (Trastek *et al.* 1985; Barrett *et al.* 1982). The splenic artery is probably progressively weakened by successive pregnancies leading to an increased frequency of these aneurysms as parity rises.

## Management

The natural history of splenic artery aneurysms is poorly understood. Moore & Lewis (1961) who monitored 14 aneurysms, found that none ruptured, but these were all arteriosclerotic aneurysms and none of the patients was pregnant. In the series described by Trastek *et al.* (1982) only one of the 34 aneurysms that were treated conservatively ruptured; this was a 7 cm aneurysm and the patient had declined elective surgery.

Once an aneurysm is suspected, most authors recommend the use of arteriography to confirm the diagnosis. This has the advantage of both localizing the lesion and of identifying whether multiple dilatations are present within the splenic or other splanchnic arteries.

Treatment in the emergency situation has usually been by splenectomy. Although splenectomy can be avoided by ligation of the aneurysm it may still be necessary for those lesions that occur close to the splenic hilum (Taylor & Woodward

1987). In elective cases, the majority are still treated by surgery although some success has been reported with embolization and this is now suggested as the treatment of choice in low risk groups (Baker *et al.* 1987; Reidy *et al.* 1990).

The principal indications for surgical intervention are symptomatic aneurysms; aneurysms in pregnant women or women of child-bearing age; lesions in any age group that are greater than 2 cm in size or ones that show a progressive increase in diameter (Trastek *et al.* 1985).

## Implications for the obstetrician

Rupture of a splenic artery aneurysm in pregnancy is exceedingly rare and the vast majority of obstetricians will retire never having seen one. The possibility of this diagnosis should always be considered in the shocked obstetric patient.

Treatment in the acute case is difficult even for experienced general surgeons. Lesions in the splenic artery proper may be treated by ligation of the splenic artery above the body of the pancreas and access is by way of the lesser sac by division of the gastro-colic omentum. Neither of these procedures is easy. The maternal and fetal mortality is so high that every effort should be made to maintain the patient's blood pressure. Temporary control of bleeding may be achieved by direct pressure on the lesser sac through the stomach until suitable assistance is available.

The splenic artery can be identified with duplex ultrasonography. Routine screening of all patients would not be practicable in view of the low overall incidence. An attempt to screen the splenic artery could be made in certain high risks groups such as grandmultiparity and those with known vascular abnormalities such as fibromuscular arterial dysplasia.

There are no guidelines on what to do in the event that a splenic artery aneurysm is identified during pregnancy. Careful consideration should be given to undertaking arteriography. It would be incorrect to withhold this investigation to avoid a very small risk to the fetus if the information obtained increased the maternal chance of survival. The timing of appropriate surgery is more difficult. If the aneurysm is small, one option would be to allow the pregnancy to continue with the patient in hospital and aim for an elective caesarean section and treatment of the aneurysm at the same time. For larger aneurysms careful surgery during the second trimester would probably be the best management.

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CLINICAL PRACTICE

# Prevalence of hepatitis B and C viruses and human immunodeficiency virus infections in women of reproductive age

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**ABSTRACT**

**Objective:** To determine the prevalence of hepatitis B and C viruses, and human immunodeficiency virus infections in women of reproductive age attending a health care system.

**Design:** Prospective cross-sectional study.

**Setting:** Public Obstetric Clinic and Service for Pre- and Perinatal Prevention of Infectious Diseases, Rome, Latium Region, Italy.

**Subjects:** 1142 women attending our centres consecutively for delivery, miscarriage, voluntary interruption of pregnancy or screening for pre- and perinatal prevention of infectious diseases.

**Interventions:** Serum samples, collected after informed consent over a period of 2 months, were tested for hepatitis B virus markers (anti-HBc and HBsAg) by enzyme linked immunosorbent assay (ELISA), for antibodies against hepatitis C virus (by ELISA and, if positive, by RIBA) and for human immunodeficiency virus antibodies (by ELISA and, if positive by Western blot).

**Results:** The seroprevalence of hepatitis B virus was 14·4% (95% CI Poisson distribution 12·2–16·5) for anti-HBc and 1·6% (95% CI, 0·9–2·5) for HBsAg. Antibodies against hepatitis C virus were detected by ELISA in 2·4% (CI 1·6–3·5) and by first generation RIBA in 0·9% (CI 0·4–1·6). Human immunodeficiency virus seroprevalence was 1·0% (CI 0·5–1·7). No significant differences were observed by age or by reason for attending.

**Conclusions:** Women attending our centres have a higher prevalence of hepatitis B virus, hepatitis C virus and human immunodeficiency virus infection than those observed in our country in larger national surveys of newborn babies, in reproductive-aged women or in other selected low-risk groups such as blood donors. This could be due to the attendance of women at increased risk such as drug addicts. The information has the additional value of emphasizing the need for adherence by health care personnel, to the recommendations issued for the prevention of occupational infections.

Surveys of selected subgroups of the population can provide an estimate of current levels and future trends of the prevalence of different infections and are an important component of prevention and control programs.

In the past, such studies have been used for the surveillance of the spread of the hepatitis B virus (HBV) but, in the last years, have become necessary to study the epidemiology of the human immunodeficiency virus (HIV) epidemic.

Population groups should be selected by expected levels of risk, public health significance and accessibility (Chin 1990, Pappaioanou *et al.* 1990).

Women of reproductive age are considered a 'sentinel group' through which to assess the spread of HIV to heterosexual populations and to define the characteristics of perinatal transmission (Allen *et al.* 1990).

In addition, data on HIV prevalence in a population attend-

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ing health care services can be used to assess the hazards of occupational infection of health care workers accidentally exposed to biological fluids from infected patients.

Hepatitis B virus and the recently identified hepatitis C virus (HCV), share with HIV similar routes of transmission and represent important potential causes of occupational infections in health care workers.

We have investigated the prevalence of HBV, HCV and HIV in women of childbearing age attending our large referral centres.

## Subjects and methods

The study has been performed in the Department of Obstetrics of St. Camillo Hospital and in the Service for Pre- and Perinatal Prevention of Infectious Diseases of L. Spallanzani Hospital, in Rome.

St. Camillo Hospital, a 1500-bed public general hospital, provides care, free of charge, to over 150 000 people each year and includes patients attending the Drug Abuse Centre located in the hospital area and those from the nearby L. Spallanzani Hospital for Infectious Diseases (with a total of more than 500 AIDS cases observed). An average of 1700 women are admitted in the Obstetric Clinic for delivery, 3500 for voluntary interruption of pregnancy and 150 for miscarriage, each year.

Since April 1, 1989 this centre has been taking part in the Regional Programme of HIV Testing at Hospital Admission for Reproductive-aged Women. Each woman has been asked to choose whether she wishes to know the result of her HIV test or whether her sample will be anonymous. Post-test counselling is offered to all women.

From October 18, 1990, we widened this programme by offering tests for hepatitis B and C serological markers.

Additionally, all tests were offered to women attending the Service for Pre- and Perinatal Prevention of Infectious Diseases of L. Spallanzani Hospital. This service attracts about 600 new attenders each year and is located in the same district as St. Camillo Hospital.

A sample size of at least 1000 women was chosen. This was recommended by Allen *et al.* (1990) on the assumption of an expected seroprevalence of HIV infection between zero and 1%.

The study was stopped on December 24, 1990 when a total of 1142 women had been tested. The women attended our centres consecutively for delivery ($n = 426$), miscarriage ($n = 45$), voluntary interruption of pregnancy ($n = 597$) or screening for prevention of infectious diseases in pregnancy ($n = 74$).

The mean age was 28·4 years (median 28, mode 29, range 14–47), without significant differences by reason for attending.

All samples were tested by ELISA for hepatitis B core antibody (anti-HBc) and, when positive, for hepatitis B surface antigen (HBsAg).

Antibodies against HCV (anti-HCV) were assayed by an HCV antibody ELISA system (Ortho Diagnostic System, USA). All reactive sera were also tested by a first-generation recombinant immunoblot assay (Chiron RIBA HCV test system—Ortho diagnostic system, USA); results have been interpreted according to the manufacturer's instructions as negative, indeterminate or positive. Antibodies against HIV (anti-HIV) were detected with a commercial enzyme linked immunosorbent assay and confirmed, if positive, by Western blot. Data have been analyzed by EPISTAT statistical package; 95% confidence intervals (CI) have been calculated using the Poisson distribution.

## Results

Anti-HBc was detected in 164 of 1142 women (14·4%; CI 95% 12·2–16·5) and more frequently in those aged over 30 years ($P < 0{\cdot}001$, $\chi^2$ test); there were 18 HBsAg carriers (1·6%; 95% CI 0·9–2·5). Anti-HCV was detected by ELISA in 28 women (2·4%; 95% CI 1·6–3·5) of which 10 were confirmed by RIBA (0·9%; CI 0·4–1·6), whilst five had indeterminate (0·4%) and 13 had negative results.

Eleven women were anti-HIV positive (1·0%; CI 0·5–1·7). Post-test counselling revealed that: six were intravenous drug users and all but one were aware of being seropositive; one was a black woman born in Uganda who had not been tested before; two others, who had never been tested for anti-HIV, were married to men who had used drugs intravenously in the past (neither of the husbands had ever been tested for HIV but were found to be seropositive subsequently); the remaining two women declined counselling. Three women had multiple infections: HBsAg plus anti-HCV, HBsAg plus anti-HIV or anti-HCV plus anti-HIV, respectively. None of the women had all three virus markers.

Table 1 shows the serological results by reason for attendance; no significant differences were observed after stratifying for age and reason for attending.

In the study period, only 11 women asked to be tested anonymously (1%): 10 were attending for voluntary interruption of pregnancy and one for delivery. In this subgroup none was positive for HBsAg or anti-HIV but one of the 11 was anti-HCV ELISA positive (RIBA indeterminate).

## Discussion

The study confirms the occurrence of hepatitis B and C viruses and of HIV in women of childbearing age attending our centres.

However, the observed prevalences are higher than those reported from other studies conducted in our country in newborn babies, women of childbearing age or other low-risk groups, such as blood donors. As an example, HBsAg carriage in Italian blood donors was 0·39% in 1990, (Angeloni P., Italian Red Cross Central Laboratory, personal communication) while the reported prevalences of anti-HCV (by ELISA) and anti-HIV were 0·87% and 0·011%, respectively (Sirchia *et al.* 1989; WHO 1990).

A 1·39% HBsAg carriage rate was observed in 44 121 pregnant women during a vaccination campaign against hepatitis B virus conducted in 1986-88 in Latium (Albertoni *et al.* 1990).

In a large national study the anti-HIV prevalence was 0·13% in newborn babies (Ippolito *et al.* 1991). The Regional Programme of HIV Testing at Hospital Admission for Reproductive-aged Women in Latium over a period of 18 months showed an anti-HIV cumulative prevalence of 0·35% in a total of 29 343 women tested (Miceli *et al.* 1990). In the same period the HIV prevalence in our centres was 0·8%, on a total of 7996 women (unpublished data).

**Table 1.** Seroprevalence of HBsAg, anti-HCV and anti-HIV in 1142 women of childbearing age by reason for attending the referral centre.

| | | Reason for attending | | | |
|---|---|---|---|---|---|
| Serology | | Delivery (*n* = 426) *n* (%) | Voluntary interruption (*n* = 597) *n* (%) | Miscarriage (*n* = 45) *n* (%) | Prenatal care (*n* = 74) n (%) |
| Anti-HBc | pos. | 48 (11·2) | 106 (17·7) | 3 (6·6) | 7 (9·4) |
| HBsAg | pos. | 4 (0·9) | 13 (2·1) | 1 (2·2) | 0 (–) |
| Anti-HCV | | | | | |
| ELISA | pos. | 9 (2·1) | 14 (2·3) | 3 (6·6) | 2 (2·7) |
| RIBA | pos. | 4 (0·9) | 3 (0·5) | 1 (2·2) | 0 (–) |
| | ind. | 0 (–) | 5 (0·8) | 0 (–) | 2 (2·7) |
| Anti-HIV* | pos. | 4 (0·9) | 7 (1·2) | 0 (–) | 0 (–) |

* ELISA and Western blot.
pos. = positive, ind. = indeterminate.

No data, to our knowledge, are currently available for the prevalence of anti-hepatitis C virus in reproductive-aged women, in our country.

The higher prevalence at the centres we studied are probably due to the attendance of women at increased risk, such as drug addicts. This is supported by the fact that in the nearby Drug Abuse Centre (which is attended by about 50% of all the drug addicts seeking public detoxication services in Latium), the prevalence of anti-HBc, HBsAg, anti-HCV and anti-HIV are about 86%, 8%, 67% and 47%, respectively (Girardi *et al.* 1990).

These differences in prevalence could be due to different risks of infection by parenteral and sexual transmission of the three viruses, to a wider spread of, and to an earlier contact with, hepatitis B virus or to the lower sensitivity and specificity of the test used to detect hepatitis C infection.

Although anonymous screening is generally considered to be more accurate because it minimizes selection bias (Chin 1990), our study shows that voluntary screening of pregnant women can be performed with a very low rate of refusal and that it offers the opportunity for counselling.

Finally, surveys based on a single hospital, even when large studies are being conducted in the same geographical area, can supply specific information on the risks to health personnel.

The data can be used, in training programmes for health care workers, to emphasize the hazard of occupational infection not only by HIV but also by other blood-borne pathogens. This should enhance compliance with anti-HBV vaccination and with the 'Universal Precautions' for the prevention of accidental exposure (Centers for Disease Control 1988).

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FERTILITY CONTROL

# Medical abortion in women of ≤56 days amenorrhoea: a comparison between gemeprost (a PGE$_1$ analogue) alone and mifepristone and gemeprost

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**ABSTRACT**

**Objective:** To determine the efficacy of a new dose regimen of vaginal gemeprost (1 mg every 6 h up to three doses) in induction of abortion in women ≤56 days gestation, and to compare this regimen with mifepristone (200–600 mg) followed 48 h later by a single dose of gemeprost (1 mg).

**Design** Two separate protocols, with 50% of the subjects randomized to one or other protocol.

**Setting** The Royal Infirmary of Edinburgh, Scotland, UK

**Subjects** 301 referred by their general practitioner or local family planning clinic, requesting termination of pregnancy at ≤56 days amenorrhoea.

**Interventions** Ongoing pregnancies and incomplete abortions were terminated surgically.

**Main outcome measures** Number of complete abortions, analgesic requirements and bleeding pattern following treatment.

**Results** Complete abortion occurred in 87% of women treated with gemeprost alone and 98% of women treated with mifepristone and gemeprost ($P$=0·0004). Analgesic requirements were greater in the group treated with gemeprost alone, compared with the group treated with mifepristone and gemeprost ($P$=0·0001).

**Conclusion** The new dose regimen of gemeprost can be used for early induced abortion, but the use of mifepristone and gemeprost has several advantages over the use of gemeprost alone.

The first descriptions of the use of prostaglandins to induce abortion included women in the first trimester (Wiqvist & Bygdeman 1970; Karim & Filshie 1970). Prostaglandins are now widely used to terminate pregnancy in the second trimester, but surgical termination of pregnancy is still the method of choice in the first trimester, since it is safe and has few long-term ill effects (Tietze & Lewit 1972; WHO 1979). The use of the natural prostaglandins to induce abortion is associated with unacceptable gastrointestinal side effects, since they have to be given in high doses because of their short half life. The 'third generation' of prostaglandins, with their longer half life, can be given in doses compatible with fewer side effects (Smith & Baird 1980; Cameron & Baird 1988).

The introduction of the antiprogesterone, mifepristone, has increased interest in medical abortion and, in combination with a low dose of prostaglandin, appears to be a safe, effective method of early termination of pregnancy (Rodger & Baird 1987; Silvestre *et al.* 1990; UK Multicentre Trial 1990). The use of mifepristone allows a smaller dose of prostaglandin to be used than when using prostaglandin alone, resulting in few prostaglandin related side effects, and lower analgesic requirements. Whilst this is apparent from data on the two methods published separately, only one small study has directly compared mifepristone and prostaglandin with prostaglandin alone, and failed by find any difference in efficacy (Cameron & Baird 1988).

In this study, the effects of a new protocol for early termination of pregnancy (≤56 days amenorrhoea) using a low total dose of gemeprost, are reported. In addition, the efficacy and side effects of this method are compared with the use of mifepristone and gemeprost at the same gestation, collected as part of a World Health Organization multicentre trial, the manuscript of which is in preparation.

## Subjects and methods

General practitioners and family planning clinics in the area were asked to refer pregnant women of ≤56 days amenorrhoea requesting abortion, and who had grounds for termination of pregnancy under the 1967 Abortion Act. Women were initially seen in the outpatient clinic, where a history was taken and a routine clinical examination performed. Once the decision to terminate the pregnancy was made, women who met the study

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criteria were offered medical termination of pregnancy. Overall 301 women were recruited into the study, which was approved by the local reproductive medicine ethics subcommittee. Written informed consent was obtained from each woman before treatment.

The first 66 women (group 1) were recruited to receive gemeprost alone (1 mg every 6 h to a maximum of 3 mg), the next 65 women (group 2) were recruited to receive mifepristone and gemeprost (200–600 mg mifepristone followed 48 h later by 1 mg gemeprost). Thereafter, a further 170 women were randomized to receive either gemeprost alone (group 3) or mifepristone and gemeprost (group 4), in the dose regimens described above. Treatment was allocated by opening a sealed envelope containing directions to one or other protocol. The envelopes were prepared in advance so that an equal number of women were randomized to each group. Neither the woman, nor the investigator was blind to the treatment method. All women were aged over 16 years, and had had no serious medical disorders and no bleeding during this pregnancy. Women who had taken the oral contraceptive pill during the cycle before, or during, conception and women with a history of irregular menstrual cycles, were excluded from groups 2–4.

### *Treatment with gemeprost alone (groups 1 and 3)*

Women were admitted to hospital on the first day of treatment (day 1). A pelvic ultrasound scan was performed to confirm the gestational age. Gestational sac diameter was recorded for subjects in group 3. Blood was taken for blood grouping, haemoglobin and serum human chorionic gonadotrophin (hCG) estimation and height and weight were recorded. The point prevalence of a series of common pregnancy or prostaglandin related symptoms was noted. A single gemeprost pessary (1 mg) was inserted into the posterior vaginal fornix. Women were instructed to remain in bed for the first hour after pessary insertion, and were then encouraged to mobilize or to sit up. Blood pressure, pulse rate and temperature were recorded every 3 h. The symptom questionnaire was repeated 6 h after the first pessary and, unless the woman had complained of severe abdominal pain, or abortion had occurred, a further 1 mg gemeprost was inserted into the posterior vaginal fornix. The process was repeated 6 h later and a third pessary was given, if necessary. The time at which bleeding and abdominal pain started and the number of episodes of vomiting and diarrhoea were noted. Analgesia was available as required; paracetamol, codeine and diamorphine were used in order for increasing severity of pain. Those who required a third prostaglandin pessary were encouraged to stay in hospital overnight. Blood was taken 24 h after prostaglandin administration for repeat measurement of the concentration of serum hCG.

Before discharge, anti-D was administered to rhesus negative women and a menstrual diary card was given to record the pattern of vaginal bleeding. Follow-up appointments were made for days 8, 15 and 29. Women were asked to use non-hormonal methods of contraception for the first post treatment cycle. Follow-up was extended until after the next menses for women in group 3.

### *Treatment with mifepristone and gemeprost (groups 2 and 4)*

On the first day of treatment (day 1) an ultrasound scan was performed, and mean gestational sac diameter recorded. Blood was taken for blood grouping and haemoglobin and serum hCG estimation, and height and weight were recorded. A single dose of 200 mg, 400 mg or 600 mg mifepristone was given, the dose being determined by random allocation. Women were allowed home immediately after taking the tablets, and given a menstrual diary card to record the pattern of vaginal bleeding.

Women were readmitted to hospital 48 h later (day 3), and a single gemeprost pessary (1 mg) was inserted into the posterior vaginal fornix. They were asked to remain in bed for 1 h after prostaglandin administration. Blood pressure, temperature and pulse rate were recorded hourly. Analgesia was administered as for patients receiving gemeprost alone. Women were allowed home after 4 h if well; some, especially those who had been given narcotic analgesia, stayed in hospital for a further few hours.

Anti-D was given to rhesus negative women before discharge. Women were given a menstrual diary card to record the pattern of vaginal bleeding, and asked to use non-hormonal methods of contraception until the first menses after treatment. Follow-up was arranged for days 8, 15, and 43, until after the first menses.

### *Follow-up (all groups)*

At the follow-up visit (day 8), the menstrual diary card was reviewed and any complications noted. A pelvic examination was performed. Blood was taken for measurement of serum hCG and haemoglobin. At the second follow-up examination (day 15) a similar protocol was employed. In addition, a pelvic ultrasound was performed. Those with an ongoing pregnancy (rising serum hCG, and a gestational sac of increasing diameter on pelvic ultrasound scan with or without an active fetal heart), underwent surgical uterine evacuation. Those few with an incomplete abortion (constant or slowly falling serum hCG and products of conception visible in the uterus on ultrasound scan) were managed conservatively or underwent surgical termination of pregnancy depending on their clinical condition. Four women given gemeprost alone were given a further pessary course, rather than undergoing surgical termination of pregnancy.

Follow-up was attempted on all women until bleeding had ceased, and the duration of bleeding noted; those in groups 2–4 were followed up until menstruation had occurred, the interval from abortion to menstruation was noted and the women were asked how the whole bleeding episode compared with their nomal menses.

### *Assays*

Haemoglobin and serum hCG measurements were made by the local haematology and reproductive endocrine laboratories respectively.

### *Statistics*

Continuous data were plotted before analysis to determine the distribution. Where the data were normally distributed, or a transformation could be employed to achieve normality, the mean and 95% confidence intervals (CI) have been quoted, and analysis of variance used to explore statistically significant differences. Otherwise, the median and range of values have been quoted, and the significance of differences between groups explored using non-parametric methods (Mann Whitney for two groups, and Kruskal Wallis for three or more groups). Categorical data are described as percentages, and the $\chi^2$ test used for statistical analysis. Throughout the next, $P$ values are described as non-significant if $P \geq 0{\cdot}05$.

## Results

There were no significant differences between the groups on the first treatment day (Table 1). The effects of treatment in groups 1 and 3, and groups 2 and 4 were initially compared. There were no significant differences in results between the women who were randomly allocated to their treatment groups and those who were not, and therefore it was considered reasonable to combine the data on women in groups 1 and 3 to allow a more powerful comparison with data on women in groups 2 and 4.

The full results of the comparisons between the group of women having the three doses of mifepristone will be published with the results of the Multicentre Trial, but there were no significant differences in abortion rate between the groups. Analgesic requirements, duration of bleeding and all other outcome measures were the same in each mifepristone dose group. Of the 150 women treated with mifepristone and gemeprost 147, (98%) aborted completely without further intervention (Table 2). One woman (who had received 400 mg mifepristone followed 48 h later by 1 mg gemeprost) had an ongoing pregnancy after treatment; this was terminated surgically 3 weeks after mifepristone administration. Two other women had a haemostatic curettage; one (following 400 mg mifepristone) in another hospital 5 weeks after the start of treatment, and another (who had received 600 mg mifepristone) underwent sterilization and curettage at her request 8 weeks after the start of treatment. In neither did histological examination of the endometrial curettings show any trophoblastic material.

Of the 151 women treated with gemeprost alone, 132 (87·4%) aborted completely (Table 2). Nine women had an ongoing pregnancy after treatment and ten had evidence of an incomplete abortion. Four of the nine women with an ongoing pregnancy opted for a further course of pessaries, three subsequently aborted completely, and one required curettage. All other women with an ongoing pregnancy or incomplete abortion underwent uterine evacuation, bringing the total to 16. None required a haemostatic curettage. The combination of mifepristone and gemeprost was significantly more effective in inducing a complete abortion than gemeprost alone, with success rates of 98% and 87% respectively ($P$=0·0004 $\chi^2$-test).

Analgesic requirements were significantly greater in women treated with gemeprost alone than in those treated with mifepristone and gemeprost ($P$=0·0001, $\chi^2$) (Table 3). There were no significant differences between the women treated with gemeprost alone and those treated with mifepristone and gemeprost for the following indices: duration of bleeding (mean 13·6 days 95% CI 12·3 to 15·0 *vs* mean 13·9 days, 95% CI 12·8 to 15·2); interval from induction of abortion to menstruation (mean 34·1 days, 95% CI 30·3 to 38·4 *vs* mean 35·8 days, 95% CI 34·5 to 37·1); and change in haemoglobin concentration from day 1 to day 8 (median −0·4g/dl, range −1·6 to 1·0 *vs* median −0·1 g/dl, range −2·9 to 1·6). There was a significant difference between the two groups for serum hCG on day 8, expressed as a percentage of the original value; (median 1·78% range 0·51 to 277·01 *vs* median 3·57%, range 0·03 to 152·6; $P$<0·0001). Since change in hCG and haemoglobin are critically dependent on the time after abortion, only data from women who attended for follow-up from day 7 to day 11 were included.

Of the 151 women treated with gemeprost alone, 117 completed the symptom questionnaire (Table 4). (The first 24 women were treated as a pilot group; of the remaining 127 women to whom the questionnaire was applied, ten failed to fill in all the details.) There was a significant increase in abdominal and pelvic pain following the first prostaglandin

**Table 1.** Characteristics of the women in each of the four groups on the first treatment day

| | Non randomized | | Randomized | |
|---|---|---|---|---|
| Variable | Group 1 (gemeprost alone) (*n*=66) | Group 2 (mifepristone and gemeprost) (*n*=65) | Group 3 (gemeprost alone) (*n*=85) | Group 4 (mifepristone and gemeprost) (*n*=85) |
| Age (years) | 26 2 (24·6 to 28·3) | 26·9 (25 3 to 28·6) | 27·0 (25·6 to 28·5) | 25·9 (24·7 to 27·2) |
| Height (cm) | 163·8 (162 4 to 165·2) | 164·9 (163·4 to 166·3) | 163 8 (162·5 to 165·0) | 164·4 (163·1 to 165·7) |
| Weight (kg) | 61·4 (57·8 to 65·0) | 62·2 (59·9 to 64·5) | 61·6 (59·7 to 63·5) | 60·0 (58·4 to 61·5) |
| Amenorrhoea (days) | 46·4 (45·0 to 47·8) | 47·7 (46 4 to 49·0) | 48·1 (47·1 to 49·2) | 46·9 (45·8 to 48·1) |
| Parous women | 50% | 52% | 40% | 46% |
| Previous pregnancy | | | | |
| >28 weeks | 35% | 42% | 29% | 41% |
| <28 weeks | 26% | 28% | 25% | 28% |
| Gestational sac diameter (mm) | (not recorded) | 19·5 (17·2 to 22·0) | 19·5 (17·8 to 21·5) | 19·6 (17·9 to 21·5) |
| Haemoglobin (g/dl) | 12·9 (12·7 to 13·2) | 13·2 (13·0 to 13·5) | 13·1 (12·9 to 13·3) | 13·1 (12·9 to 13·2) |
| hCG (i.u/l) | 38 650 (339 to 214 900 | 47 720 (2103 to 154 900) | 38 510 (1389 to 210 700) | 43 870 (1038 to 191 000) |

Data are expressed as means (95% CI) except for parity (%) and medians (range) for serum human chorionic gonadotrophin (hCG) concentration. There were no significant differences between any of the four groups.

**Table 2.** Initial outcome of treatment with gemeprost alone or mifepristone and gemeprost*

| Outcome of treatment | Gemeprost alone ($n$=151)<br>% of women (95% CI) | Mifepristone and gemeprost ($n$=150)<br>% of women (95% CI) |
|---|---|---|
| Complete abortion | 87·4 (84·7–90·1) | 98·0 (96·9–99·1) |
| Ongoing pregnancy | 6·0 (4·0–7·9) | 0·7 (0·0–3·9) |
| Incomplete abortion | 6·6 (4·6–8·6) | 1·3 (0·6–5·0) |

*The two women in the mifepristone and gemeprost group who required a haemostatic curettage are included as incomplete abortions. Data are expressed as percentage of women (95% CI).

pessary in women treated with gemeprost alone, and a significant decrease in breast tenderness (Table 4). There was no change in the occurrence of headache, vomiting, indigestion, loss of appetite, constipation, faintness, tiredness, or dysuria following gemeprost.

The lower overall success rate of 87% in the group of women treated with gemeprost alone would preclude routine clinical use. To determine whether there were any factors which might predict outcome, characteristics of 'successful patients' (those who aborted completely after gemeprost without further intervention) and 'unsuccessful patients' (those who failed to abort completely after gemeprost) were compared (Table 5). The median (range) number of episodes of vomiting and diarrhoea were 0 (0–5) and 0 (0–6) in the group who aborted completely following gemeprost, and 0 (0–3) and 0 (0–4) in the group who failed to abort (ns).

Women who aborted completely following treatment bled a median (range) time of 300 minutes (90–720) after the first prostaglandin pessary, significantly earlier than those who failed to abort, at 360 minutes (165–765) after gemeprost ($P<0·05$). Abdominal pain occurred at a median (range) of 195 (20–540) minutes after the first pessary in those in whom the procedure was successful, compared to 180 (110–420) minutes after the first pessary in those who did not abort (ns). Those who aborted following treatment had a significantly greater requirement for analgesia than those who failed to abort ($P<0·003$); 58% of the 'unsuccessful' required no analgesia compared to 19% of the 'successful' treatments.

## Discussion

This study demonstrates a greater success rate of mifepristone and gemeprost in early legal abortion, compared to the use of gemeprost alone. These results contrast with a smaller study of 49 women, where 1 mg of gemeprost every 3 h to a total of five pessaries was as effective as 150 mg of mifepristone daily for 4 days and 1 mg gemeprost on the third treatment day (Cameron & Baird 1988). The lower analgesic requirement in women treated with mifepristone and gemeprost, compared to those treated with gemeprost alone confirms previous results (Cameron & Baird 1988). Analgesic requirements appear to be directly related to the total dose of prostaglandin, whether women are pretreated with mifepristone (Rodger *et al.* 1989); or given gemeprost alone: 53% of women receiving up to 5 mg gemeprost required opiate analgesia (Cameron & Baird 1988) compared with 36% of the women in the present study who received up to 3 mg gemeprost. A 0·5 mg gemeprost pessary is as effective as 1 mg gemeprost in combination with mifepristone but results in significantly less abdominal pain (Rodger *et al.* 1989).

In the present study there was no significant difference in the efficacy of 200, 400 or 600 mg mifepristone in combination with 1 mg gemeprost; these data are in agreement with a preliminary report on all 1188 women in the multicentre trial, stating the three treatment regimens to be equally effective (Maurice 1991). In a previous study we were unable to demonstrate any significant differences in efficacy between 600, 500 or 400 mg mifepristone (Rodger & Baird 1987) and a WHO supported trial showed that repeated small doses of mifepristone (5 × 25 mg) were as effective as a single 600 mg dose (WHO 1991). Although the data sheet for mifepristone recommends a single 600 mg dose followed 48 h later by 1 mg gemeprost, the present study suggesting that 200 mg dose is effective points to the need for further research to determine the lowest effective dose of mifepristone and prostaglandin.

Haemoglobin levels, hCG levels and duration of bleeding have all been assessed in relation to the first day of treatment (day 1), although most of the abortions occurred on day 1 in the gemeprost alone group, and on day 3 in the mifepristone and gemeprost group. Median hCG concentrations were lower 7 days after the start of treatment in the group treated with gemeprost alone, compared with the group of women treated with mifepristone and gemeprost, despite the fact that the former group includes a greater proportion of women with an ongoing pregnancy. In women treated with gemeprost alone, a significant decrease in hCG concentration is seen 24 h after treatment, whereas in women treated with mifepristone and gemeprost, hCG does not decline until prostaglandin is given (day 3) and abortion occurs (WHO 1989). The difference in

**Table 3.** Analgesic requirements in women treated with gemeprost alone or with mifepristone and gemeprost.

| Analgesia | Gemeprost alone ($n$=151) | Mifepristone and gemeprost ($n$=150) |
|---|---|---|
| None | 24% | 45% |
| Paracetamol only | 7% | 16% |
| Codeine ± paracetamol | 33% | 18% |
| Diamorphine ± codeine ± paracetamol | 35% | 21% |

Significance of difference between the two groups $P=0·0001$.

**Table 4.** Point prevalence of pregnancy/prostaglandin related symptoms at 0, 6 and 12 h after the first prostaglandin pessary in 117 women treated with gemeprost alone.

| | Time in relation to first pessary (h) | | |
|---|---|---|---|
| Symptom | 0 | 6 | 12 |
| Dowsiness | 18 (15%) | 34 (29%)* | 36 (31%)** |
| Nausea | 38 (32%) | 43 (37%) | 21 (18%)* |
| Abdominal distension | 12 (10%) | 26 (22%)* | 25 (21%)* |
| Abdominal pain | 12 (10%) | 85 (73%)** | 67 (57%)*** |
| Pelvic pain | 7 (6%) | 34 (29%)**** | 30 (26%)**** |
| Diarrhoea | 4 (3%) | 24 (21%)**** | 11 (9%) |
| Breast pain | 42 (36%) | 26 (22%)* | 19 (16%)** |
| Weakness | 15 (13%) | 30 (26%)* | 29 (25%)* |
| Hot flushes | 1 (1%) | 17 (15%)*** | 12 (10%)*** |

Data are expressed as numbers of women and percentages in brackets.
Significance of difference between symptoms at time 0, * P <0·02, ** P<0·001, *** P <0·002, **** P <0·0002.

hCG concentrations between these two groups reflects the later occurrence of abortion in women treated with mifepristone and gemeprost. The change in hCG concentration 7 days after prostaglandin administration in each group might have been a more valid comparison. Otherwise, the effects of both treatments in terms of duration of bleeding and interval to next menses (both measured from the start of treatment rather than the day of abortion)) were remarkably similar.

Previous protocols using gemeprost in early legal abortion in this centre have employed a regimen, with a total dose of up to 5 mg prostaglandin (Smith & Baird 1980; Cameron & Baird 1988). This regimen, of 1 mg every 6 h to a total of 3 mg gemeprost was chosen in an attempt to reduce prostaglandin side effects. Although a direct comparison with surgical abortion was not made here, the relatively low complete abortion rate of 87% associated with prostaglandin-induced abortion supports the conclusion from smaller studies that vacuum aspiration under general anaesthesia is more effective than medical termination of pregnancy using gemeprost alone (Smith & Baird 1980).

The increase in the prevalence of prostaglandin related side effects following the first pessary (nausea, abdominal pain, hot flushes and diarrhoea) is expected, the significant decrease in breast tenderness presumably indicates a fall in hormonal levels as separation of the conceptus and abortion occurs.

The lower mean weight of women who aborted after treatment suggests that the dose/kg and/or the plasma profile of gemeprost is important, perhaps resulting in a greater 'prostaglandin impact' in women who aborted successfully after treatment with gemeprost (Csapo 1972). Despite a greater height and a lower weight in women who aborted after gemeprost alone, there was no difference in body mass index (weight/height$^2$, Quetelet's index). This contrasts with published data on the predictors of failed attempted abortion with the antiprogesterone mifepristone, with or without prostaglandin (Grimes *et al.* 1990). There was no significant difference in mean gestation in women who aborted, compared to those who did not. The earlier interval to bleeding and the increased analgesic requirement in women who aborted after prostaglandin therapy suggests a greater sensitivity to prosta-

**Table 5.** Characteristics of women who aborted completely after gemeprost alone (successful), compared to those who did not (unsuccessful). Data are expressed as means (95% CI), except for parity (percentage) and medians and range for: initial hCG, hCG on day 2 and day 8 and change in haemoglobin concentrations. The probabilities of a significant difference is shown in the last column as determined by analysis of variance, except for parity ($\chi^2$ test), and hCG, change in serum hCG and change in haemoglobin conentrations (Mann-Whitney *U* test).

| Variable | Successful (*n*=132) | Unsuccessful (*n*=19) | *P* | Significance test |
|---|---|---|---|---|
| Age (years) | 25·6 (24·2 to 27·1) | 24·3 (22·3 to 26·42) | ns | ANOVA |
| Height (cm) | 163·9 (162·8 to 164·9) | 157·87 (146·3 to 169·5) | <0·05 | ANOVA |
| Weight (kg) | 61·3 (59·3 to 63·3) | 68·1 (57·5 to 78·7) | <0·05 | ANOVA |
| Gestation (days) | 47·7 (46·8 to 48 6) | 45 0 (42·7 to 47·4) | ns | ANOVA |
| Parity | 45% | 32% | ns | $\chi^2$ |
| Serum hCG | | | | |
| Initial value (iu/v) | 38 960 | 31 150 | ns | Mann-Whitney |
| % of initial value | (339–214 000) | (706–136 500) | | |
| On day 2 | 34·1 (7·8 to 126·7) | 58·9 (28·5 to 103·2) | <0·0001 | Mann-Whitney |
| On day 8 | 1·7 (0·5 to 113·6) | 90 7 (0·9 to 277·0) | <0·0001 | Mann-Whitney |
| Change in Hb | | | | |
| (day 1–day 8) (g/dl) | −0 3 (−1·6 to 1·0) | −0·5 (−1·4 to 0·2) | ns | Mann-Whitney |

Data are expressed as means (95% CI) except for parity (%) and medians (range for serum human chorionic gonadotrophin (hCG) levels and change in haemoglobin (H6) concentrations.

glandin in these women. The greater decrease in serum hCG in women who do abort is apparent as early as 24 h after treatment ($P<0{\cdot}0001$).

These data show clear advantages of mifepristone and prostaglandin in early legal abortion compared to prostaglandin treatment alone. Most women undergoing termination of pregnancy using gemeprost alone who required all three pessaries had an overnight stay in hospital, which is not only inconvenient for many women, but has obvious cost implications. This was not a feature of termination of pregnancy using mifepristone and gemeprost. The lower analgesic requirement in women receiving the combination of mifepristone and gemeprost implies lower perceived pain, and therefore greater patient acceptability, than the use of gemeprost alone. Mifepristone and gemeprost is likely to be the method of choice for early medical abortion, but where mifepristone is unavailable or contraindicated, 1 mg of gemeprost every 6 h may provide a useful alternative.

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REPRODUCTIVE SCIENCE

# Higher multiple births and the modern management of infertility in Britain

## For the British Association of Perinatal Medicine

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**ABSTRACT**

**Objective** To assess prospectively the number of triplet and higher multiple births born in 1989 and their methods of conception. To assess obstetric factors and the effect of these pregnancies on neonatal medical services.

**Design** All consultant paediatricians received a monthly card asking whether they had been involved in the management of triplet and higher multiple pregnancies delivered after 22 weeks gestation. Detailed questionnaire sent to those giving a positive response.

**Setting** British Paediatric Surveillance Unit organized mailings to all members of the British Paediatric Association working in the British Isles.

**Subjects** 156 pregnancies resulting in 482 babies (143 triplets, 12 quadruplets and 1 quintuplet set). These data were compared to nationally collected OPCS data.

**Main outcome measures** Method of conception, obstetric performance, neonatal outcome.

**Results** Of the 156 pregnancies, 47 (31%) were conceived naturally, 52 (34%) had ovarian stimulation (usually with clomiphene or gonadotrophins) 37 (24%) had IVF and 17 (11%) GIFT. All quadruplet and quintuplet pregnancies were established after assisted reproduction. Mothers who had had IVF were significantly older than those who had ovulation induction alone. The median gestation at birth was 33 weeks. Overall 181 (40%) of the babies required intensive care for a median duration of 5 days. The perinatal mortality of the triplets alone and quads and quins together was 70 and 104 per 1000 respectively.

**Conclusions** Assisted reproduction is the major cause of triplets and higher multiple births and ovarian stimulation is the single most important technique currently in use. These babies are very likely to be born pre term and make considerable demands on neonatal intensive care facilities.

There has been a very marked increase in the number of triplets born in England and Wales since the late 1970s (OPCS Birth Statistics 1979, 1988), as well as a fourfold increase in the number of higher multiple births (quadruplets, quintuplets and sextuplets) born between 1971 and 1985 compared with the 15-year period 1956-1970 (Botting *et al.* 1987). Since 1985 there appears to have been a further steep increase in the numbers of higher multiple births born in Britain.

The reason for this dramatic increase is thought to be new methods for treating the infertile couple. Concern expressed in Parliament has led to the promulgation of Interim Licensing Authority guidelines in relation to *in vitro* fertilization (IVF) which stipulates that no more than three embryos should be replaced at any one time (Royal College of Obstetricians and Gynaecologists, 1990). Ovarian stimulation with clomiphene, gonadotrophins and other hormones followed by natural conception is not, however, similarly regulated and is thought to be in much more widespread use than IVF.

Attempts have been made to investigate the effects of some of these treatments on the numbers of higher multiple births. The Medical Research Council Working Party (1990) published the outcome of 1267 pregnancies conceived by IVF and found that only 4% of the pregnancies resulted in triplets and higher multiple births. Also recently published is a retrospective study of 'triplets and higher order births' (Botting *et al.* 1990) which attempted to ascertain all these multiple births over a 5-year period in the early 1980s and to investigate both the medical and social problems faced by these babies.

The implications of the increasing numbers of higher multiple births on the newborn services have caused concern to both obstetricians and neonatologists, and the British Association of Perinatal Medicine proposed that a prospective survey be undertaken for one calender year in an attempt to establish

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the size of the problem, the contribution that modern methods for treating infertility makes on higher multiple births and the implications for neonatal services. This paper is a report on that survey.

## Subjects and methods

For the whole of the calendar year 1989, consultant paediatricians in the British Isles were asked every month whether they had been involved in the management of triplets or higher multiple births. Enquiry was made by postal contact through the British Paediatric Surveillance Unit (BPSU). The BPSU sends a monthly enquiry card to all consultant paediatricians asking whether they have seen any one of a number of relatively rare conditions in the preceding calendar month. The clinician ticks the relevant box or makes a nil notification response and returns the postcard to the BPSU office. The BPSU agreed to include triplets and higher multiple births as one of the eight conditions surveyed in 1989.

On receipt of a positive response, the BPSU notified one of us (J.W.) of the name of the responding paediatrician and our office sent out three questionnaires to the clinician. One was for the paediatrician who looked after the babies, and the paediatrician was asked to send on a second and third form to the obstetrician who was responsible for the management of pregnancy and labour and to the gynaecologist who may have been involved in the management of infertility. We anticipated that for some pregnancies the gynaecologist and obstetrician would be quite separate, possibly working in different hospitals and even different cities. If a response had not been obtained within 1 month of the pregnancy being notified to us, a reminder was sent and eventually telephone contact was made to encourage completion of the forms.

In early 1990, as a further check to ensure that as many pregnancies as possible had been ascertained, a letter was sent to all consultant neonatologists in the British Isles listing the names of the mothers who had given birth to triplets or higher multiple births in their hospital and whom they had notified to us. We asked them to check these names against their admission registers to ensure that this was a complete list of such babies cared for in 1989. We then sent out a further set of forms for any subsequent notifications.

As a further cross check on the accuracy of our survey, we obtained from the OPCS the numbers of triplets and higher multiple births born in England and Wales and from the Registrar General's Office the numbers for Scotland for the year 1989. The OPCS agreed to compare their multiple birth data for England and Wales with ours for evidence of systematic bias in reporting. For this comparison our data were broken down into three variables: Regional Health Authority, maternal age and birthweight of the infant. Unfortunately, our data were collected by health region where the baby was born, whereas the OPCS data refers to the region where the mother is resident.

Statistical comparisons were made using *t*-tests for continuously distributed variables and the $\chi^2$ or Mann-Whitney tests for categorical variables.

## Results

We were advised of 160 multiple pregnancies through the BPSU. Follow-up questionnaires revealed that 30 of these were duplicate notifications from different hospitals or clinicians. A further five notifications were made in error. Thus a total of 125 notifications of actual cases were received. In addition to these cases a further 15 were notified directly to us by paediatricians and not through the BPSU. As a result of our final letter to consultant neonatologists, a further 22 pregnancies, not previously notified, were found. A total of 162 pregnancies were ascertained by these methods but, in six of these, we could obtain no information at all from the clinicians despite repeated letters and telephone calls. This report is based on 156 triplets and higher multiple births. In 19, complete data sets were not received. There was one missing neonatal form, two missing gynaecology forms and 18 missing obstetric and gynaecology forms. In only two instances was this due to specific refusal on the grounds of confidentiality.

### *Methods of conception*

There were 143 sets of triplets, 12 quadruplets and one quintuplet set. This represents a total of 482 babies. We were notified of the method of conception in 153 of the 156 pregnancies. Table 1 summarizes these data. In 47 (31%) spontaneous conception occurred, in 52 (34%) various methods of ovarian stimulation were used, in 37 (24%) the pregnancy occurred after *in-vitro* fertilization (IVF) and in 17 (11%) pregnancy was achieved as a result of gamete intra-fallopian transfer (GIFT).

The commonest method of ovarian stimulation was with clomiphene (27 pregnancies) or with menopausal gonadotrophins or follicle stimulating hormone (FSH) (17 pregnancies). Two women received clomiphene and FSH together and in six the obstetrician did not inform us of which drugs were used for ovarian stimulation. In 15 of the 37 women in the IVF group, we could not obtain information on the number of embryos inserted. Three embryos were inserted in 16 women, but five had four embryos replaced and one had two embryos and two

**Table 1.** Method of conception in 156 triplet and higher multiple pregnancies

| Method of conception | Triplets | Quads & quins |
|---|---|---|
| Natural conception | 47 | 0 |
| Ovarian stimulation | 44 | 8 |
| In vitro fertilization | 36 | 1 |
| 2 embryos | 1* | 0 |
| 3 embryos | 15 | 1 |
| 4 embryos | 5 | 0 |
| Unknown number | 15 | 0 |
| GIFT | 14 | 3 |
| 2 ova | 1 | 0 |
| 3 ova | 3 | 0 |
| 4 ova | 6 | 3 |
| 5 ova | 0 | 0 |
| 6 ova | 1 | 0 |
| Unknown number | 3 | 0 |
| Unknown method of conception | 3 | 0 |
| Total | 144 | 12 |

* Refers to the same woman who had two ova replaced together with two embryos.

ova (simultaneous IVF and GIFT). Table 1 shows the number of ova replaced in the GIFT procedure. The median number was 4 (range 2–6). No pregnancy involving quadruplets or quintuplets occurred spontaneously. In eight, the pregnancy occurred following ovarian stimulation (clomiphene in two, gonadotrophins in six, one of which also received buserelin and another one received also clomiphene) three were established after GIFT with four ova and one after IVF treatment with three embryos. In one case we could not ascertain the treatment method. Whereas ultrasound monitoring of follicular development was universal in IVF or GIFT procedures, it had been used in only 22 of the 49 pregnancies established after ovulation induction where the gynaecologist gave us the information (Table 2). When clomiphene was given, ultrasound monitoring had been used in only 6 of the 26 pregnancies and in only one of the three where quadruplet pregnancy ensued. In contrast, ultrasound monitoring had been used in 11 of the 13 pregnancies that followed menopausal gonadotrophin treatment and in 5 of the 6 where FSH was used (in three, quadruplets occurred despite the use of ultrasound monitoring). It is of interest that neither the number of follicles seen or the average or total dose of menopausal gonadotrophin given correlated with the occurrence of a quadruplet pregnancy. The commonest (modal) dose of menopausal gonadotrophin (Pergonal) was two ampoules a day (mean 3·3) but higher doses were not uncommon; in one case 10 ampoules a day. Twelve ampoules was the commonest (modal) total dosage, with a mean of 22. In one case a total of 70 ampoules were used (1 ampoule contains 75 units each of FSH and LH).

## *Obstetric performance*

Table 3 shows some obstetric variables in triplet pregnancies and compares spontaneous conception with assisted reproduction. Women in the assisted reproduction group were older than those in the spontaneous group ($P$=0·044, $t$-test). Women who had IVF (mean 31·2, SD 3·9 years) were significantly older than women who had ovulation induction alone (mean 29·2, SD 4·4 years) ($P$=0·04, $t$-test). In the assisted reproduction group, women with quadruplets were delivered at a mean gestation of 29·9 (SD 3·9) weeks which was significantly earlier than those having triplets who were delivered at a mean gestation of 32·3 (SD 2·9) weeks ($P$=0·009 $t$-test).

The occurrence of hypertension (systolic blood pressure >140 mmHg or diastolic >90 mmHg) at the last clinic visit was similar in both groups (29% in the assisted reproduction group and 33% in the spontaneous group). One woman in the spontaneous group developed fulminating pre-eclampsia at 31 weeks and there was some delay in delivering her because of difficulty in finding a neonatal intensive care unit that would accept her babies. She developed severe intravascular coagulopathy and died 8 days after delivery.

**Table 2.** Use of ultrasound for monitoring follicular development in pregnancies that followed ovulation induction

| Method of ovulation induction | $n$ | Ultrasound scan Used | Not used |
|---|---|---|---|
| Clomiphene | 26 | 6 | 20 |
| Human menopausal gonadotrophin | 13 | 11 | 2 |
| FSH | 6 | 5 | 1 |
| Not specified | 4 | 0 | 4 |
| Total | 49 | 22 | 27 |

Table 4 shows social class differences between the assisted and spontaneous groups (classified according to the husband's occupation, or mother's occupation if unmarried) for the subgroup of triplets. The association between social class was compared (I–III *vs* IV–VI) with the method of conception for all triplet pregnancies where the data were available. Only 27% of the parents in the upper (I–III) social class group had spontaneous conception compared with 46% of those in the lower (IV–VI) social class group. This was a statistically significant difference ($\chi^2$ 4·05, $P$ <0·025).

The maternal body mass index (BMI = kg/m$^2$) at first booking visit was available for 67 of the triplet pregnancies and this correlated significantly with the gestational age at delivery ($r$ = 0·23, $P$=0·33). If the BMI was <19 then the mean gestational age at delivery was 31 weeks compared with delivery at 33·5 weeks if the BMI was >35.

## *Neonatal factors*

Maturity at birth and birthweight are shown in Figs 1 and 2. The median gestational age at birth was 33 (range 24–37) completed weeks and the median birthweight was 1700 g (range 340–3330 g). The median gestational age at birth for the triplets was 33 weeks and for the quadruplet and quintuplet sets was 31 weeks. This difference is statistically significant ($P$=0·02 Mann-Whitney $U$ test).

There were 50 perinatal deaths (10·2%) of which seven were stillborn and 43 babies died before discharge from hospital. The perinatal mortality rate (PNMR) for all the triplets and higher multiple births (five stillbirths after 28 completed weeks and 31 first week neonatal deaths) was 77 per 1000.

Amongst the triplet sets there were 384 babies born alive and 45 deaths (seven stillbirths and 38 babies died before discharge from hospital). The median gestational age of the deaths was 26 weeks (range 24–36 weeks) and the median age at death was 2 days (range 1–95 days). The calculated PNMR for trip-

**Table 3.** Obstetric factors for triplet pregnancies only, in natural conceptions and assisted reproduction

| | Natural conceptions | | Assisted reproduction | |
|---|---|---|---|---|
| Variable | $n$ | Mean (SD) | $n$ | Mean (SD) |
| Maternal age (years) | 44 | 29·0 (4·2) | 84 | 30·7 (4·4) |
| Maternal height (cm) | 28 | 163·3 (6·8) | 49 | 162·1 (6·8) |
| Weight at booking (kg) | 38 | 66·7 (10·9) | 73 | 63·5 (11 8) |
| Weight gain during pregnancy (kg) | 35 | 11·1 (5·7) | 64 | 12·9 (5·9) |

Data are expressed as means (SD).

**Table 4.** Method of conception by social class. The social class is dependent on the husband's occupation or the mother's if she is single

| Social class | *n* | Natural conception (%) | Assisted reproduction *n* | (%) |
|---|---|---|---|---|
| I | 7 | (15) | 14 | (14) |
| II | 10 | (21) | 28 | (29) |
| III | 5 | (11) | 17 | (18) |
| IV | 5 | (11) | 11 | (11) |
| V | 1 | (2) | 2 | (2) |
| VI | 11 | (23) | 7 | (7) |
| Not available | 8 | (17) | 18 | (19) |
| Total | 47 | | 97 | |

lets was 70 per 1000. There were 53 babies born as part of a quadruplet or quintuplet set and 11 (20%) died before discharge from hospital (there were no stillbirths). The median gestational age of the babies who died was 25 (range 24–29) weeks and the median age of death was 7·5 days. The PNMR for quadruplets and quintuplets was 104 per 1000.

In 34 (22%) pregnancies the woman was referred to a perinatal centre for delivery. It was necessary to transfer out at least one of the multiple sibship on 13 occasions (involving 17 babies) because the neonatal unit in which the babies were to be admitted was full. In 15 of 149 cases where information was available, the receiving neonatal unit needed to hire or borrow equipment in order to look after the infants. The maxium level of care required by the individual member of the multiple birth sibship was known in 457 cases. 181 (40%) needed Level I (Intensive) Care, 234 (51%) Level II (Special) care and 42 babies did not require admission to a neonatal unit and were nursed by their mothers. In 110 pregnancies the number of infants already receiving intensive care prior to admission of the multiple birth cohort was known. The median number of infants already receiving Level I (Intensive) care was 5 (range 0–27). Overall 154 (45%) of 346 babies where information was available required mechanical ventilation for a median duration of 5 (range 1–104) days. The median length of stay in a neonatal unit for the cohort of multiple birth infants was 25 (range 1–171) days.

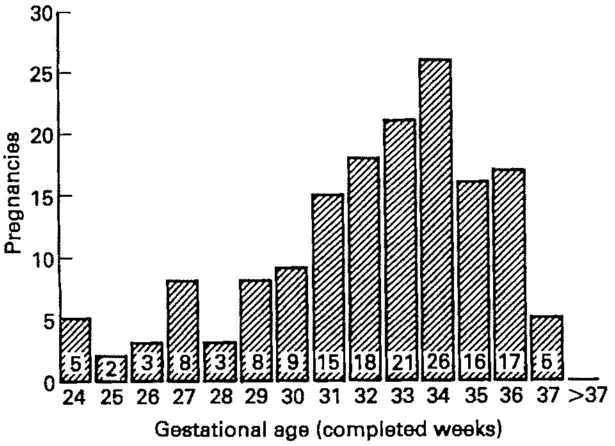

**Fig. 1.** Range of gestational ages for all the reported pregnancies. The vertical axis refers to the actual numbers and the number of pregnancies in each group is shown in each column.

Thirteen of the cohort babies had congenital anomalies; four considered minor and five severe (Table 5). Three of the neonatal deaths were associated with major congenital anomalies. All of the obvious congenital anomalies were amongst triplet sets. The risk of major congenital anomalies compared with the method of conception is shown in Table 6. The risk was greatest in naturally conceived pregnancies.

According to official Government figures for 1989, there were 210 sets of triplets, quadruplets and quintuplets notified from England, Wales and Scotland (OPCS Birth Statistics 1989; Annual report of the Registrar General for Scotland 1989). There were 196 sets of triplets, 13 sets of quadruplets and one quintuplet set. We ascertained 12 sets of quadruplets and the single set of quintuplets. There were 195 sets of triplets and higher multiple births born in England and Wales in 1989 notified through the vital registration mechanism. We were notified of 139 sets of triplets born in England and Wales. In two sets of triplets born before 28 completed weeks, one of the fetuses was stillborn and would not have been counted as a triplet set in the vital registration statistics, If these two sets are excluded then we were notified of 72% of all cases born in England and Wales. On comparison of the regional health authority in which the infants were born, there was fairly good agreement with the regions in the north of England, but the four Thames regions and the Wessex region showed a very poor relation. When maternal ages are compared for all English health regions, there is 75% agreement for women aged 25-29 years, but this is less good (50% agreement) for women older and younger than these. There was very good agreement between our data and OPCS figures for infants with birthweight below 2500 g (70–75% agreement) but this was less close for heavier babies.

## Discussion

Triplets and higher multiple births are now a more frequent event in Britain. This is the first prospective study of the scale of the problem and its relation to the modern management of infertility. We have ascertained from paediatricians responsible for the care of these infants approximately 75% of all the cases in England, Scotland and Wales in one year (which we

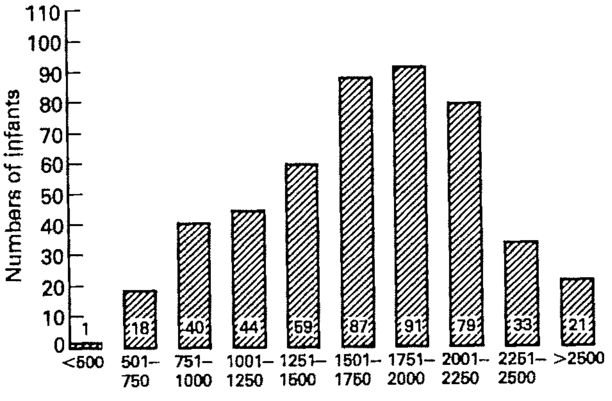

**Fig. 2.** Range of birthweights for the reported infants. The vertical axis refers to the actual number of infants and the number of infants is shown in each column.

**Table 5.** Major congenital malformations noted in the cohort of infants

| Malformation | *n* |
|---|---|
| Oesophageal atresia with tracheo-oesophageal fistula | 2 |
| Meconium ileus | 1 |
| Beckwith's syndrome | 1 |
| Down's syndrome | 1 |
| Complex congenital heart disease | 1 |
| Major deformity of ear | 1 |
| Posterior urethral valves | 1 |
| Unspecified | 1 |
| No data available | 27 |
| Babies without malformations | 446 |

have then compared with official Government figures). There appears to be relatively little systematic under-reporting to us compared with OPCS figures when the data for England and Wales is considered. In particular, the figures for low birthweight infants are representative. It is very difficult to compare the data for English regional health authorities in and around London as there are so many transfers across regional boundaries.

There are a number of possible reasons for the under-reporting by consultant paediatricians. It is probable that pregnancies ending before the babies are considered by obstetricians to be viable are not notified to their paediatric colleagues. Unfortunately there is no organized system in Britain that could obtain information prospectively on these pregnancies from obstetricians. A second possible reason for the under-reporting is that paediatricians did not complete the BPSU forms reliably. In 1989 the BPSU reported that 89% of paediatricians returned the cards on a monthly basis, but it is possible that the accuracy of the response is unreliable. The fact that 37 of the 162 (23%) pregnancies we discovered were not notified through the BPSU supports this possibility. As far as we know this is the first crosscheck between BPSU and a reliable source and raises the question as to how accurate the returns are.

Although it has been assumed that the increasing use of methods for treating the infertile couple is the cause of the marked increase in higher multiple births, there is no information on the precise contribution of each of these methods to the total numbers in a geographical area. We have found that in only 30% of triplet or higher multiple births did conception occur naturally. In almost half of the pregnancies where assisted reproduction was used, ovarian stimulation rather than the more sophisticated IVF or GIFT procedures was used. Clomiphene is reported to cause multiple ovulation, but was the most commonly used drug in this study. This is in keeping with the knowledge that clomiphene is very widely used for treating infertility, even being prescribed by general practitioners while their patients are on the infertility clinic waiting list. In a review of published studies by Scialli (1986) the risk of multiple gestation was estimated at 8–13% in pregnancies induced by clomiphene. The use of gonadotrophins to stimulate ovulation is reported to be associated with a 15–45% risk of twins or more and a 5–6% risk of triplets (Scialli 1986). The low rate of follicular monitoring with ultrasound when ovulation is induced (44% of cases) is perhaps a cause for concern, although there was no evidence in this study that the number of follicles present affected the outcome, at least in terms of quadruplets rather than triplets. IVF was used in just under one quarter of our cohort and with this technique the risk of multiple births is reported to be 22% (Medical Research Council Working Party 1990; Australian In-Vitro Fertilization Collaborative Group 1988). The risk is likely to be related to the number of embryos inserted and in 5 of the 22 cases where we know the number of embryos replaced, four were inserted. This was not strictly against the recommendations of the Voluntary Licensing Authority which stated 'no more than three eggs or pre-embryos should be transferred in any one cycle unless there are exceptional clinical reasons where up to four may be replaced per cycle'. It seems unlikely that 'exceptional clinical reasons' could be found in over 20% of notified cases and furthermore, gynaecologists did not tell us of the number of embryos replaced in 41% of IVF pregnancies. GIFT is a relatively new technique, the use of which remains outside the Human Fertilisation and Embryology Act (1990) providing the couples own gametes are used. The risk of multiple births with this technique is reported to be 19–38% (Medical Research Council Working Party 1990; Craft *et al.* 1988). In this study, just over 10% of higher multiple births were associated with the use of GIFT. It is likely that the use of GIFT will increase due to its requirements for relatively low technology and lower cost. In more than half the GIFT pregnancies, four or more ova were replaced and in three this led to a quadruplet birth. The Medical Research Council Working Party (1990) has recently reported that 80% of all the GIFT and IVF pregnancies in Britain occurred after treatment in just three centres; all of which operated outside of the National Health Service. In addition, we have shown that patients in higher social classes (I–III) were significantly more likely to give birth to triplets following assisted reproduction compared with natural conception. This presumably relates to the very limited availability of some forms of assisted reproduction to women treated within the National Health Service. Those babies who require intensive care and who have been conceived in private institutions in our clinical experience all received care in cots funded by the National Health Service.

The lack of significant differences between the natural and assisted reproduction groups differ from the findings of the Medical Research Council Working Party on Children Conceived by IVF (Medical Research Council Working Party 1990); this may have been due to the preponderance of babies conceived by induction of ovulation and GIFT in our study. These techniques are simpler than IVF and induction of ovulation is much cheaper. They are therefore more likely to be used first in women with relatively short-term infertility who are more likely to be representative of the total population than women receiving IVF. This is supported by the fact that

**Table 6.** Number of babies with congenital malformations by type of conception

| | Method of conception | | | |
|---|---|---|---|---|
| Malformation | Natural | Ovarian stimulation | IVF | GIFT |
| Major (*n* = 9) | 5 | 3 | 1 | 0 |
| Minor (*n* = 4) | 3 | 1 | 0 | 0 |

women in our study having IVF were significantly older than women having ovulation induction alone.

The median gestational age at which birth occurred was 33 weeks and the median birthweight of the individual babies was 1700 g. The maturity at birth in this study is comparable with other reports (28–34·8 weeks) of highly selected series of triplet pregnancies (Collins & Bleyl 1990; Lipitz *et al.* 1989, 1990; Sasson *et al.* 1990; Vervliet *et al.* 1989). Despite these babies being relatively large as a group, there were a significant number born small enough to cause considerable strain on the neonatal services. Almost half of the babies required mechanical ventilation, and the median time required for this form of treatment was 5 days. The majority of neonatal intensive care units in Britain are relatively small with intensive care facilities for six or fewer infants. The intensity of the workload is high and many of the available neonatal intensive care cots are usually occupied. The median numbers of occupied neonatal intensive care cots at the time the triplets or higher multiple birth sibships were admitted to the unit was five, thereby causing an immediate and severe strain on resources if the new babies required close attention. In 13 multiple birth sibships, individual babies had to be separated from their siblings (and presumably their parents) and transferred to other hospitals. Some hospitals found it necessary to borrow or hire extra equipment to look after the babies. Although it is relatively easy to obtain additional equipment at short notice, it may be extremely difficult to get extra medical and nursing staff to look after these babies. It is apparent from this survey that the increase in triplets and higher multiple births is placing a significant additional strain on already stretched neonatal services. It is perhaps a little surprising that only 22% of these pregnancies were referred to recognized perinatal centres for delivery and neonatal care. This problem is highlighted by the tragic case of the maternal death where an identified factor in her death was a delay in transfer of the woman in labour with triplets because a perinatal unit could not be found that had facilities available for the care of three potentially ill immature infants.

We have expressed mortality as perinatal mortality rates which for triplets and quadruplets was 70 and 104 per 1000 total births respectively. We do not believe that these figures are particularly helpful as many of the babies who died, did so well after the first week of life and are therefore excluded from these figures. In addition, comparison of the British PNMR with those from other countries may be misleading as the definition may vary from nation to nation. Values for PNMR have, however, been reported for triplet pregnancies and for the most recent time period (1985–88) Newman *et al.* (1989) gave a figure of 50 per 1000. Less recent figures for England and Wales (1975–83, excluding 1981) reported a PNMR of 165 and 220 per 1000 total birtths for triplets and quadruplets respectively (Botting *et al.* 1987).

In conclusion we have confirmed the progressive and very steep rise in triplet and higher multiple births in Britain. More than two thirds of these pregnancies occur as the result of the treatment of infertility and are associated with a perinatal mortality rate at least seven times the figure for Britain as a whole. If the current expansion of assisted reproduction facilities in the private sector continues, the contriubtion of multiple pregnancy to preterm delivery and maternal and perinatal mortality will surely continue to increase. Positive steps to limit this increase should include rigorous enforcement of the guidelines of the Interim Licensing Authority that only three embryos should be replaced at any one time. Recently, the Royal College of Obstetricians and Gynaecologists (RCOG) has recommended that no more than three oocytes should be replaced when GIFT is undertaken (Royal College of Obstetricians and Gynaecologists 1990). Improvements in the technique of ovulation induction to reduce the incidence of high multiple ovulation are urgently required. More and better follicular tracking should be useful in this regard and this has also been recommended by the RCOG (1990). In cases where multiple conception occurs despite gynaecologist's best efforts, consideration might also be given to selective fetocide to reduce the incidence of higher multiple births (Wapner *et al.* 1990). We support the Royal College of Obstetricians and Gynaecologists in their recommendation that detailed counselling about the problems of multiple pregnancy should be given to all couples prior to their enrolment in a programme of assisted reproduction. One recent study found that only 53% of women undergoing assisted reproduction understood that multiple birth was a possibility (Botting *et al* 1990). We suggest that counselling should include written information with wording agreed by both the obstetric and gynaecological and the paediatric professional bodies. Consideration might also be given to making private medical insurance a compulsory part of private treatment for assisted reproduction to cover the cost of any neonatal intensive care that may be necessary (Levene 1991). Apart from the medical problems associated with multiple pregnancies it must not be forgotten that there is a considerable social and financial cost to their families (Botting *et al.* 1990) which is often unrecognized.

## Acknowledgments

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CASE REPORTS

# Invasive cervical disease following large loop excision of the transformation zone

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## Case report

A 25-year-old woman attended our colposcopy clinic in September 1989 with a 3-month history of abnormal cervical cytology. The presenting smear had been reported as severe dyskaryosis. The patient was 24 weeks pregnant at the time of examination. Colposcopic assessment showed no characteristics to suggest invasive disease and biopsy was delayed until after delivery. She was examined again at 10 weeks post-partum when her smear was still abnormal and colposcopy suggested a diagnosis of cervical intraepithelial neoplasia (CIN) 3. Large loop excision of the transformation zone (LLETZ) was performed and CIN 3 was confirmed. No comment concerning completeness of excision was possible because of diathermy artefact at the apex of the excision specimen.

Review 6 months later revealed a normal fully visible transformation zone and her smear was negative, but she was pregnant once more (20 weeks) and a final review was planned for 3 months post-partum. This was performed in March 1991. A small area of acetowhite epithelium was noted and a directed biopsy was taken; this confirmed CIN 3. The smear obtained at the same time showed borderline nuclear abnormalities only. As a result of the biopsy a further large loop excision as performed. This confirmed Stage Ia2 carcinoma of the cervix (maximum depth 2·8 mm, maximum lateral dimension 4·6 mm). All of the biopsy and cytological material has been reviewed and the original reports confirmed.

## Discussion

Over the last 2 years there have been several reports and published correspondence regarding the use of LLETZ in the management of women with abnormal cervical smears and CIN (Prendiville *et al.* 1989; Luesley *et al.* 1990). Among other advantages this technique has been shown to demonstrate the presence of occult invasion in excised cervical transformation zones thus enhancing the safety of management. This feature has been emphasized to such an extent that many would now consider discharging patients to a cytology surveillance programme after treatment if invasive disease has been excluded and one negative cytological and colposcopic examination has been performed. There is considerable debate as to the optimal setting for cytological follow-up following treatment for CIN (Giles *et al.* 1989; Lopes *et al.* 1990).

Whilst it is possible that the sequence of events in our patient might indicate a new lesion we feel that this is unlikely and that the last biopsy must represent progression of residual disease that was not removed by the first excision. Pregnancy may have influenced the natural history of this lesion and, cetainly, rendered the first follow-up assessment less than optimal. Of most concern is that in many units throughout the UK such a patient would have been discharged from colposcopic surveillance, either after initial treatment or after her first normal follow-up. Re-referral might have been prompted by the subsequent smear yet this was only reported as borderline.

We are not aware of any published reports of invasion after treatment with LLETZ, although invasion after laser and cryocautery has been described. One important difference is that diagnosis in the former is based on the examination of a large excision that is unlikely to miss evidence of invasive disease whereas with laser and cryocautery diagnosis is usually based on a small directed biopsy.

We recommend that any cytological abnormality, no matter how minor, be regarded as an indication for colposcopic reassessment if there has been prior treatment and that patients should only be discharged if colposcopic examination and cytology are negative in the non-pregnant state.

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# The treatment of microscopic residual ovarian cancer with intraperitoneal interferon: a clinical and flow cytometric study

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## Case report

A 29-year-old woman presented in 1981 with post-coital bleeding and an abnormal smear. Colposcopy was negative and a diagnostic cone biopsy was performed. Histology of the specimen revealed a well differentiated Stage Ia papillary adenocarcinoma of the cervix which was treated by extended total abdominal hysterectomy; both ovaries were preserved.

In February, 1988, a mass at the vaginal vault was noted at routine follow-up. At laparotomy, a mobile 10 cm × 12 cm right ovarian tumour was found. Frozen section examination of the neoplasm suggested a primary serous papillary adenocarcinoma; this was later confirmed on paraffin sections. A radical oophorectomy, consisting of a bilateral salpingo-ophorectomy, infracolic omentectomy, multiple biopsies and washings, was carried out. Peritoneal washings taken at the time of laparotomy contained adenocarcinoma cells, but diaphragmatic brushings were negative. The tumour was staged as Stage 1c according to the FIGO criteria. Comparison with sections from the cone biopsy in 1981 did not suggest concordance between the two tumours.

Intermittent chlorambucil (10 mg/day) was given for a total of 12 weeks, but although at subsequent laparoscopy no macroscopic abnormality was identified, peritoneal washings were again positive. After five cycles of intraperitoneal carboplatin (400 mg/m$^2$ every 4 weeks), peritoneal washings still contained malignant cells. Laparoscopy was otherwise normal, as were abdominal and pelvic CT scans.

In August, 1989, she began treatment with intraperitoneal α-2 interferon (Intron A, Kirby-Warwick). Fifty million units were instilled in 1·5 litres of warmed dialysate via a Tenchkoff catheter, weekly for 16 weeks. Before each course of treatment peritoneal washings were taken for cytological and flow cytometric examination.

Toxicity predominantly consisted of influenza-like symptoms: fever, fatigue and muscular aches. While most of these symptoms abated within 72 h each week, fatigue persisted throughout the period of treatment. Haematological toxicity is shown in Fig. 1.

Viable adenocarcinoma cells disappeared from the peritoneal washings after the first week of therapy. On two subsequent occasions (weeks 5 and 8), there was difficulty distinguishing viable malignant cells from dead tumour cells and mesothelial cells.

Flow cytometric multiparameter analysis of the peritoneal washings revealed a pretreatment DNA diploid cell population. In addition, a second, near-diploid, tumour cell population was suspected from the high coefficient of variation (CV, 6·78) and a skewed GO/G1 peak. The analysis of tumour-associated antigen and oncoprotein expression showed that epidermal growth factor receptor (EGFR) expression was moderately high before treatment but became strikingly elevated after the first week of interferon therapy. After two weeks of treatment, however, there was a dramatic fall in EGFR expression and this coincided with a change in the DNA histogram as the near-diploid population disappeared and the CV fell (4·23–4·86). Only low levels of tumour-associated antigens and transmembrane oncoprotein, c-erbB-2, were found before therapy (Table 1).

Serum CA 125 levels fell rapidly to within normal limits (Fig. 2). The patient remains in complete remission, with a normal serum CA 125, 28 months after completing treatment.

## Discussion

In advanced ovarian cancer, combination chemotherapy given after initial debulking surgery is often unsuccessful in completely eradicating disease (Neijit et al 1984; Dembo 1986). Adjuvant therapy may prolong survival in patients with early stage disease (Young et al. 1990). However, if there is residual tumour after chemotherapy, the effective treatment of epithelial ovarian cancer is seldom achieved (Berek 1989).

Theoretically, intraperitoneal administration of drugs may offer a pharmacological advantage over the intravenous route

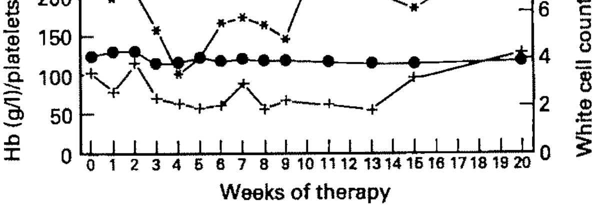

**Fig. 1.** Effect of intraperitoneal α-interferon treatment on haematological indices: (●) haemoglobin (Hb); (+) white blood cells; (∗) platelets.

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**Table 1.** Tumour associated antigen and oncoprotein expression (in arbitary fluorescence units) in cells retrieved from peritoneal washings during intraperitoneal α-interferon therapy)

| | Week of therapy | | | | |
|---|---|---|---|---|---|
| Marker | 0 | 1 | 2 | 4 | 16 |
| EGFR | 65 | 195 | 33 | 28 | 13 |
| C-erbB-2 | 36 | 30 | 69 | 51 | 38 |
| C-myc | 42 | 35 | 6 | 26 | 2 |
| SM3 | 7 | 10 | 28 | 0 | 3 |
| CA 125 | 24 | 84 | 48 | 43 | 3 |
| HMFG1 | 35 | 18 | 22 | 6 | 17 |

EGFR = epidermal growth factor receptor.
HMFG1 = human milk for globulin 1.
SM3 = stripped mucin 3.
C-erbB-2 and c-myc are oncoproteins.

in the management of ovarian cancer (Los & McVie 1990). However, data from several studies suggest that worthwhile responses are limited to patients with minimal residual (< 5 mm) or microscopic disease (Berek *et al.* 1985; Howell *et al.* 1987. Nardi *et al.* 1990). Methods to optimize this approach include the use of combinations of cytotoxic agents, and the instillation of biological response modifiers, in particular α-interferon.

Berek *et al.* (1985) first reported the use of intraperitoneal α-interferon for the treatment of ovarian cancer. The rationale for this approach was supported by *in vitro* studies which suggested a specific cytostatic and cytolytic role for this agent against ovarian carcinoma cells (Epstein *et al.* 1980; Allavena *et al.* 1982). Subsequently, a significant increase in peritoneal 'natural killer cell' activity has been demonstrated after the intraperitoneal administration of α-interferon (Lichtenstein *et al.* 1988). Four of 11 patients had complete remission confirmed surgically; all four had disease less than 5 mm in diameter. There was no benefit observed in those with more extensive disease (Berek *et al.* 1985). Despite the promise of this first report and confirmation from another small study (Willemse *et al.* 1989), no larger studies have been initiated to better define the role of intraperitoneal α-interferon alone in microscopic ovarian cancer. Others have, however, begun to use it in combination intraperitoneal therapy (Nardi *et al.* 1990).

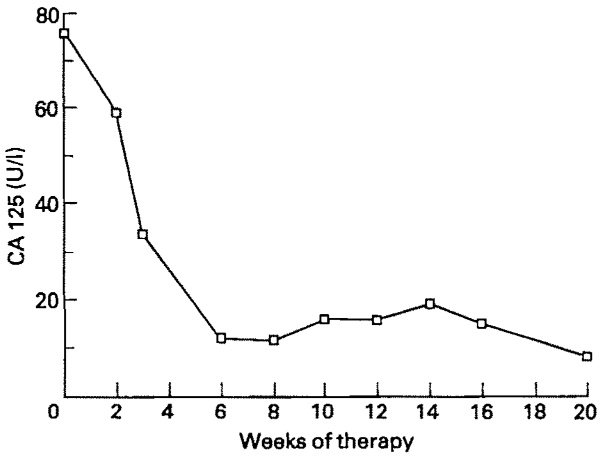

**Fig. 2.** Serum CA 125 levels (normal range < 30 units/litre) during intraperitoneal α-interferon therapy.

Monitoring response to such treatment may be difficult. Conventional cytology of peritoneal fluid may be misleading (Sagae *et al.* 1988). Furthermore, serum CA 125 levels may be normal in the presence of microscopic disease (Welander *et al.* 1988). It has been suggested that flow cytometric DNA analysis is an accurate method for the detection of malignant cells within peritoneal washings and may augment cytological examination (Lovecchio *et al.* 1986; Sinton *et al.* 1990). However, the value of these measurements is limited in the absence of a tumour cell population with a DNA content that is clearly distinguishable from the normal diploid population. This was illustrated in this case when pretreatment analysis of DNA content did not clearly separate an abnormal cell population. Hence, measurement of other variables, such as oncoprotein expression, has been employed in an attempt to increase sensitivity. In this report, the initial rise followed by a spectacular drop in EGFR expression shortly after the start of treatment coincided with a disappearance of tumour cells, as determined by cytological examination and suspected from flow cytometric DNA analysis, thus providing further evidence of response. Therefore, multiparameter flow cytometry in conjunction with classic immunocytology may be a powerful tool for the study of cell subpopulations in these heterogenous cell systems (see Commentary by van Dam & Lowe in this issue of the Journal p. 545).

Despite having early stage disease (1c), a dismal prognosis was predictable for our patient. This report confirms that intraperitoneal α-interferon may be used successfully for the treatment of microscopic ovarian cancer remaining after optimal chemotherapy, and that, even when high doses are used for a sustained period, this treatment has acceptable toxicity. Further studies of its use are therefore warranted. These should be accompanied by the assessment of more sensitive techniques for monitoring response, such as single and multiparameter flow cytometric assays.

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# Primary serous carcinoma of the female peritoneum. Report of a case with a re-examination of a histogenetic problem based on the use of a specific antimesothelial-cell antibody

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## Case report

A 75-year-old woman was admitted because of ascites, weight loss, nausea and severe asthenia of 2-month duration. Her health had been good. She had worked as a wool weaver in a textile factory for more than 30 years. Radiological studies, including ultrasound and computerized tomography of the abdomen, were non-contributory. The finding of malignant epithelial cells in the ascitic fluid suggested a possible metastatic involvement of the peritoneum from an unknown primary carcinoma. At laparotomy, almost 4 litres of haemorrhagic fluid were removed from the peritoneal cavity and abdominopelvic carcinomatosis was apparrent. Widespread tumour implants were found on both the visceral and parietal peritoneum and the omentum. A partial surgical debulking was performed, consisting of total hysterectomy, bilateral oophorectomy and omentectomy together with biopsies of two neoplastic nodules on the lower surface of the liver. Postoperatively the patient received chemotherapy with 5-fluorouracil (600 mg/m$^2$/week for 12 cycles) and she was still alive but with abdominal progression of the residual tumour 5 months after surgery.

Histologically, all the tumour implants showed the appearance of an invading tubulo-papillary carcinoma. The neoplastic epithelium, which occasionally showed a clear transition with the mesothelial layer (Fig. 1), ranged from cuboidal to columnar cells. In some areas these showed PAS-diastase positive and hyaluronidase-resistant Alcian-blue positive cytoplasmic staining, mostly in the form of globules. The malignant epithelium showed positive immunostaining for low-molecular-weight cytokeratin (LMWC), epithelial membrane antigen (EMA) and B72.3, whereas it was negative for carcinoembryonic antigen (CEA) and vimentin. The same immunohistochemical profile was also found in the normal mesothelium contiguous to the tumour but with the exception of negative reactivity for B72.3. In addition, the mesothelium showed cytoplasmic immunostaining, mainly of diffuse distribution, following incubation with a primary polyclonal antibody specifically directed against mesothelial cells. However, this antibody also marked the apical cytoplasmic portion of the malignant PAS-diastase- and Alcian-blue-negative cells of serous type (Fig. 2).

## Comment

This case is of interest not only because of the rare occurrence of primary serous carcinoma of the female peritoneum (Clement *et al.* 1989), but also because it allowed us to verify the purported usefulness of immunohistochemistry in distinguishing this neoplasm for both serous carcinomas of the ovary and diffuse malignant peritoneal mesotheliomas of epithelial type (Bollinger *et al.* 1989; Truong *et al.* 1990; Khoury *et al.* 1990). In addition, the availability of a recently developed polyclonal antibody specifically directed against mesothelial cells (Donna *et al.* 1986) was helpful in investigating the still controversial histogenesis of this neoplasm.

A variety of antibodies have been investigated recently in an attempt to define an immunophenotypic profile exclusive to peritoneal serous tumours and which would be of value for diagnostic purposes. However, no single discriminating antibody has been reported up to now and also the use of panels of several antibodies has not been rewarding in all the cases. A combination of immunoreactivity for EMA and CEA has been claimed to support a diagnosis of serous tumour (Raju *et al.* 1989), but a positive CEA does not necessarily exclude a mesothelioma (Jones 1987). An association of S-100 and B72·3 or placental alkaline phosphatase (PLAP) positivity has been described as being effective in distinguishing serous peritoneal tumours from diffuse mesothelioma in at least 90% of specimens (Bollinger *et al.* 1989). Leu-M1, CEA and/or B72·3 positivity in a peritoneal tumour has recently been reported to favour a diagnosis of serous tumour (Truong *et al.* 1990) but some peritoneal serous neoplasms do not stain for any of these three antibodies. The equivocal results of our immunohistochemical study (in particular CEA– and B72·3+) further support the view that clinical information, such as age and sex, distribution of the tumour and the light microscopy resemblance of the tumour to ovarian serous neoplasms are still the main criteria for recognizing peritoneal serous carcinomas and distinguishing them from peritoneal malignant mesotheliomas.

The pathogenesis of serous peritoneal carcinomas has been a subject of controversy. They were originally included in a spectrum of papillary tumours of peritoneum, which also encompassed mesotheliomas of both well-differentiated and diffuse type (Foyle *et al.* 1981). In contrast, according to a different view, they arise from ovarian surface epithelium with subsequent intraperitoneal spread (McCaughey 1985). Other authors (August *et al.* 1985) have claimed that serous peritoneal carcinoma are different from both primary ovarian carcinomas and mesotheliomas, since they derive from mesothelial cells under a müllerian influence. The antimesothelial cell antibody used in the present case, gave an immunostaining reaction pattern like that observed previously in ovarian carcinomas of mixed serous and mucinous type (Donna *et al* 1986), in which a positive staining was seen only in the serous cells. This result, although only from a single case, can be regarded as evidence for a mesothelial origin of the serous peritoneal carcinoma. However, the process of epithelial differentiation during the neoplastic growth results in a partial loss of the original mesothelial antigenic imprint which persists exclusively in the apical portion of the cytoplasm of serous cells.

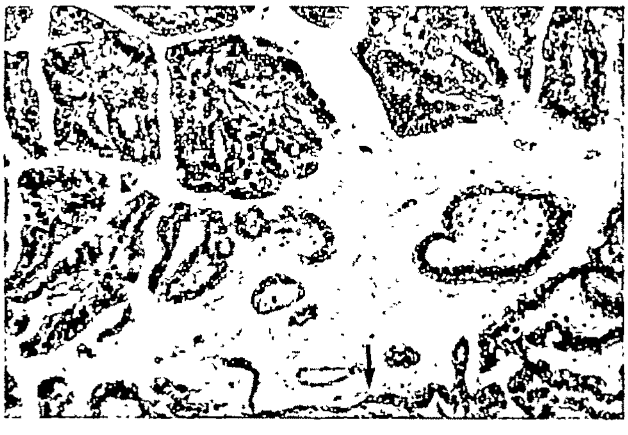

**Fig. 1.** The characteristic papillary pattern of the peritoneal serous carcinoma. Note the transition (arrow) from the normal flat mesothelium to the neoplastic columnar epithelium (H&E, × 120).

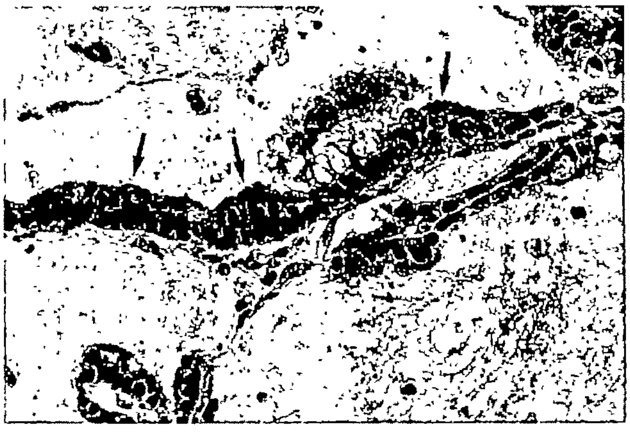

**Fig 2.** The antimesothelial-cell antibody stains the apical surface (arrows) of the malignant epithelium of serous type, whereas the mucinous cells are not labelled (Peroxidase-antiperoxidase, × 400).

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# Diagnosis of the placental antecedents of pre-eclampsia

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## Case report

A 38-year old woman had had three early miscarriages and two pregnancies complicated by severe proteinuric pre-eclampsia ending at 26 and 34 gestational weeks, respectively. Her only other significant problem was of bronchial asthma. In view of her obstetric history she was prescribed low dose aspirin (75 mg daily) before starting a planned pregnancy; she conceived on this regimen which continued throughout her pregnancy. She had an uneventful pregnancy until the 23rd gestational week when she complained of non-specific mild abdominal pain for a few days. The rate of growth of the fetal abdominal circumference (AC), which until then was above the 50th centile (Campbell 1976), fell, with almost no growth until the 25th week (Fig. 1a) and subsequent recovery to normal growth along the 25th centile. A similar growth pattern of the fetal head circumference was also observed (data not shown). Sonographic examination of the placenta failed to reveal any structural changes. A rise in the resistance index (RI) of the umbilical artery flow velocity waveforms to above normal (Cohen-Overbeek & Campell 1989) coincided with the fall in the AC growth (Fig. 1b). The changes in both fetal growth and umbilical artery flow velocity waveforms were confirmed by multiple serial readings. The RI remained constantly high until the 27th gestational week and then returned to normal. In addition, at 25 weeks the maternal plasma concentration of Von Willebrand factor (VWF), a marker of vascular endothelial cell damage (Editorial 1988), increased (Fig. 1c). Neither the platelet count nor the kaolin-clotting times changed significantly. The pregnancy continued uneventfully until the 30th week when, despite the low-dose aspirin, proteinuric pre-eclampsia developed. The hypertension was controlled with methyldopa and nifedipine. After the onset of pre-eclampsia the rate of growth of the AC declined slightly while both the umbilical artery RI and the VWF concentrations increased further (VWF values above 500% are considered abnormal in pregnancy [unpublished data]) (Fig. 1c). An emergency lower-segment caesarean section was performed at 34 weeks and 3 days because of worsening pre-eclampsia with an early HELLP syndrome (haemolysis, elevated liver enzymes and low platelets). A live baby boy was born in good condition weighing 1877 g (10th centile for the normal Oxford population, Yudkin *et al.* 1987). The mother made an uneventful recovery. Histology of the placenta revealed the presence of an old subchorionic infarct 3 cm in diameter and 0·7 cm thick in one marginal cotyledon.

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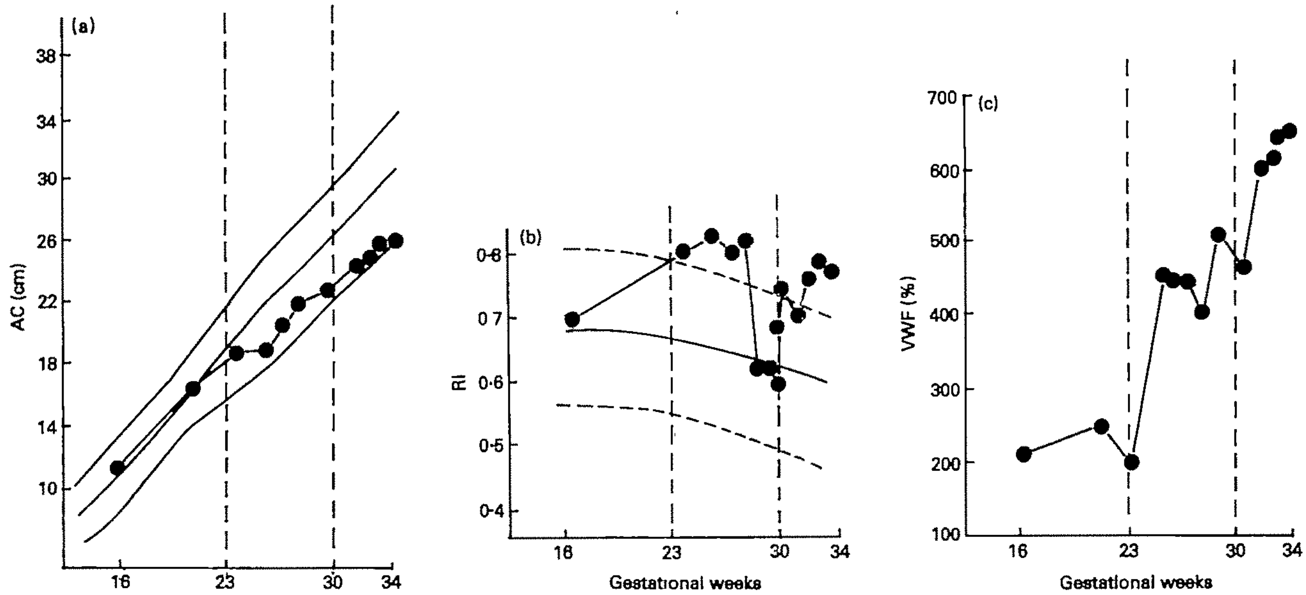

**Fig. 1.** (a) Fetal abdominal circumference (AC) growth pattern, (b), Umbilical artery resistance index (RI), and (c) maternal concentration of plasma Von Willebrand factor (VWF) in a patient who was thought to have a placental infarction at 23 weeks and who developed proteinuric pre-eclampsia at 30 weeks. The mean (2 SD) of the normal reference values for the AC (Campbell 1976) and the RI (Cohen-Overbeek & Campbell 1989) in pregnancy are also shown in (a) and (b), respectively.

## Discussion

Pre-eclampsia is thought to originate in the placenta (Redman 1991) but there is no consistent way of detecting the early pathology which is believed to comprise uteroplacental circulatory insufficiency secondary to structural defects of the spiral arteries supplying the intervillous space.

In our patient the time courses of the fetal and maternal changes coincided. This could have been a chance event or else it could have arisen from pathology in the organ common to both—namely the placenta.

The feto- and utero-placental circulations can be assessed non-invasively by Doppler ultrasound techniques. In growth-retarded fetuses, placental insufficiency has been associated with increased resistance to blood flow in the feto-placental circulation (Burke *et al.* 1990). Placental abruption can also be associated, in some instances, with changes in the utero-placental flow velocity waveforms (Degani *et al.* 1990; Oosterhof & Aarnoudse, 1991). However, only gross placental abnormalities are sonographically evident and, even with high-resolution ultrasound, placental infarctions are hard to detect because most are isoechoic to viable placenta (Harris *et al.* 1990).

There is evidence that diffuse endothelial damage underlies the maternal syndrome of pre-eclampsia (Roberts *et al.* 1989). VWF is primarily a product of injured endothelial cells which mediates platelet adhesion to endothelium (Takeuchi *et al.* 1988; Editorial 1988). Raised levels of VWF in the maternal circulation are a feature of pre-eclampsia (Roberts *et al.* 1989).

It is increasingly evident that the concept of placental ischaemia as the cause of pre-eclampsia, which has been under consideration for many years (Page 1948), is likely to be correct (Redman 1991). With this in mind the interpretation of the sequence of events in this woman could be that the placental infarct occurred at 23 weeks and caused the abdominal pain as well as the subsequent disturbances in the maternal and fetal measurements. One could speculate that an area of transient vasoconstriction surrounding the placental infarction could have been responsible for the increased placental vascular resistance and reduced fetal growth detected after that time. The change in maternal VWF might be related to release of a factor or factors toxic to maternal endothelium secondary to reduced trophoblastic perfusion, as proposed by Roberts *et al.* (1989), or activation of maternal platelets, which are an alternative source of VWF (Editorial 1988). If the latter were correct it would fit with the concept of early activation of maternal platelets in the genesis of pre-eclampsia (Redman 1990), but would imply that low-dose aspirin is sometimes ineffective as anti-platelet therapy. a problem recorded previously (Ahmed *et al.* 1991). If this interpretation of these data is correct then we would suggest that the trigger to the maternal and fetal problems was a placental infarct occurring at about 23 weeks with partial recovery; followed by further placental ischaemia leading to proteinuric pre-eclampsia and the eventual preterm delivery.

This case also supports the view that antepartum improvement of umbilical artery flow velocity waveforms may occur (Hanretti *et al.* 1988; Brar & Platt 1989), presumably reflecting spontaneous recovery following an acute insult to the feto-placental circulation.

Pre-eclampsia can give rise to various changes in fetal and maternal physiology. This case report illustrates one sequence for the development of pre-eclampsia but many others may account for the different clinical presentations of this polymorphic syndrome. We present this report because it may alert others to similar cases and so help to clarify the sequences of events that antedate clinically severe pre-eclampsia.

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## SHORT COMMUNICATION

# Identification of multiple trisomy using DNA polymorphisms

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The rate of early pregnancy failure is probably greater than 50% (Edmonds *et al.* 1982). Early pregnancy loss is frequently associated with chromosomal abnormalities, in particular trisomy. Rates of chromosomal abnormality are often extrapolated from karyotyping of material obtained at amniocentesis, chorion villus sampling or miscarriage. From this the commonest aneuploidies appear to be those of the sex chromosomes and trisomy 16 (Boue *et al.* 1975). Trisomy of other chromosomes is seen less frequently. Initially, this suggests that non-disjunction rates are highest for the sex chromosomes and chromosome 16. It is likely however, that the apparent rates of aneuploidy are spurious since pregnancies complicated by other trisomies miscarry at a very early stage, before clinical recognition, and therefore escape such studies. Boue *et al* (1975) found no examples of trisomy 1 in material from 1500 miscarriages, yet Brandriff *et al.* (1987) reported two spermatazoa with chromosome 1 non-disjunction in a series of 18 hyperhaploid spermatazoa. It is probable that non-disjunction of chromosome 1 occurs with the same frequency as that of other chromosomes but since it is the largest chromosome and carries the greatest number of genes, trisomy 1 pregnancies fail even before implantation.

Until recently no methods existed for karyotyping of gametes; however, the introduction of the human-sperm hamster-egg system has allowed direct inspection of human sperm chromosomes. Using this technique Martin *et al* (1987) found an overall rate of sperm chromosomal abnormalities of 10·4%, with aneuploidy 4·7% Similarly, obtaining oocytes for karyotyping is difficult. Wramsby *et al.* (1987) karyotyped 23 'spare' oocytes from women undergoing ovarian stimulation. Of these, 12 were found to be aneuploid. Extrapolation from these numbers suggest that embryonic single aneuploid should occur in about 60% of conceptions and double aneuploidy in about 8% of conceptions.

In their study of 1500 miscarriages, Boue *et al.* (1975) found trisomy in 52%, with double trisomy in 2% Larger multiple trisomies were not seen. Multiple chromosomal abnormalities are, however. very rarely identified by cytogenetic analysis. Karyotyping products of conception after miscarriage may fail in up to 50% of cases (Henderson *et al.* 1991). This is often due to infection in the material sent for culture but may also be because cells carrying more complex chromosomal abnormalities do not grow well in culture.

The use of DNA analysis circumvents the need to establish cell culture and can directly identify the presence of additional chromosomes and their parental origin. This can be done by the use of variable number tandem repeat (VNTR) DNA markers (see review by Bennett & Moore 1991). VNTRs consist of a single DNA motif repeated many times and arranged sequentially at a particular chromosomal location. The number of repeats is highly variable, differs between individuals, and usually between the two chromosomes in one individual. If DNA is digested using a restriction enzyme, Southern blotted and hybridized to a probe specific for the VNTR locus then, in heterozygous individuals, two restriction fragments will be identified. The difference in the size of these two fragments

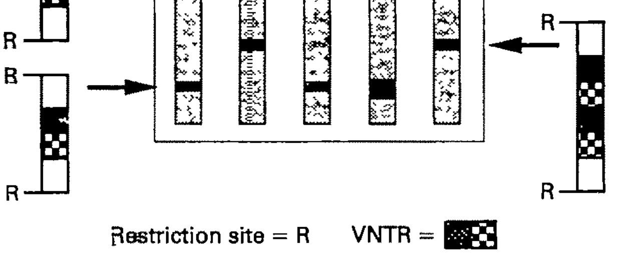

**Fig. 1.** Use of VNTR (variable number tandem repeat) probes in the diagnosis of trisomy The presence of a variable number of tandem repeats at a single locus means that the distance between two restriction recognition sites (R) is different on each of the four parental chromosomes. After digestion with the restriction enzyme, Southern blotting and hybridization to probe which detects the VNTR, each parent shows two bands. The normal child (N) also shows two bands, one from each parent. The trisomic child shows either three bands (Ta), one from one parent and two from the other, or two bands (Tb) with a double dose of one band from one of the parents.

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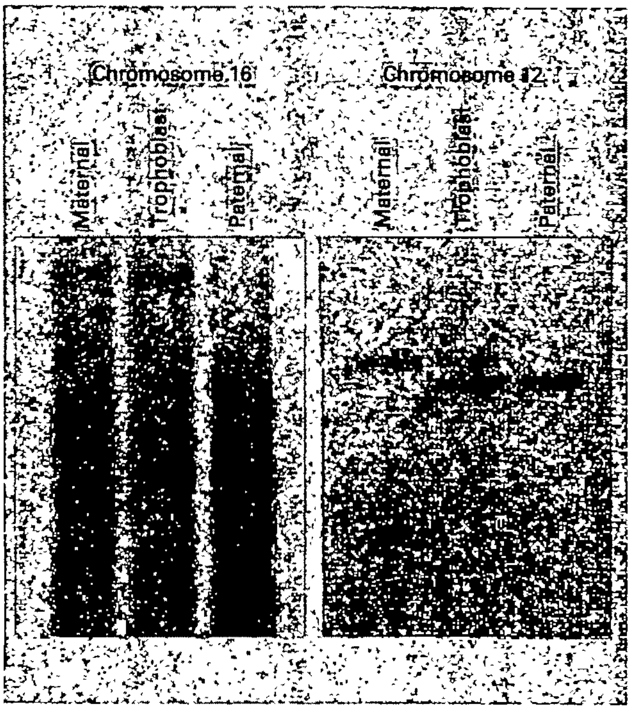

**Fig. 2.** Southern blot analysis of paternal, maternal and trophoblast DNA using the chromosome specific VNTR probes p79-2-23 (chromosome 16) and MS43 (chromosome 12). The trophoblast has inherited an additional maternal chromosome 16 band indicating trisomy. A similar pattern, but with an extra paternal band, was seen with the probes p5-1-29 (chromosome 2) and p9 (chromosome X) (not shown). In the case of chromosomes 7 and 12 the trophoblast has inherited a 'double dose' of the paternal band. If the DNA is present in equal copy numbers the larger molecular weight band should be slightly denser than the smaller molecular weight band. In this case the smaller molecular weight band is denser, and similar in density to the homozygous paternal band, indicating trisomy.

will be a reflection of the difference in the number of tandem repeats on the two chromosomes. The high degree of polymorphism of VNTRs means that a couple are unlikely to share restriction fragment lengths. Their offspring will normally inherit one restriction fragment from each parent. Trisomic offspring may inherit either an additional restriction fragment or a double dose of one of the usual two depending upon whether non-disjunction has occurred at the first or second meiotic division and whether or not recombination has taken place at the VNTR locus (Fig. 1). By using a VNTR probe specific for each, it is possible to identify both a single trisomy of any chromosome and multiple trisomies.

As an example, we describe an anembryonic pregnancy in which trisomy of four autosomes and one sex chromosome were identified using chromosome specific polymorphic DNA markers.

## Case report

A 24-year-old primigravida had light vaginal bleeding after 5 weeks of amenorrhoea. Real-time ultrasound examination suggested an anembryonic pregnancy and a repeat scan one week later confirmed the diagnosis. The pregnancy was terminated by suction evacuation under general anaesthesia. The evacuated trophoblast was stored dry at −20°C together with 10 ml of maternal and paternal blood in EDTA tubes.

DNA was prepared from the evacuated trophoblast, and from maternal and paternal blood, using standard techniques. The restriction enzymes *Hinf I*, *Taq I* and *Pst I* were used to digest 4 μg of DNA. The DNA was then size fractionated by agarose gel electrophoresis and transferred to Hybond N (Amersham International UK) nylon filters by Southern blotting. The filters were hybridized to a battery of chromosome specific VNTR probes. After high stringency washing, autoradiography was performed overnight using intensifying screens.

For most of the chromosomes the trophoblast had inherited one restriction fragment from each parent, but probes specific for chromosomes 2, 16 and X showed that the trophoblast had inherited three bands, and for chromosomes 7 and 12 there were double doses of one band. The additional chromosomes 2, 7, 12 and X were of paternal origin while the additional chromosome 16 was of of maternal origin (Fig. 2).

## Comment

Our investigation of this pregnancy imply the fertilization of an oocyte carrying non-disjunction for chromosome 16 by a spermatocyte carrying non-disjunction of chromosomes 2, 7, 12 and X. Although trisomy 16 appears to be the most common aneuploidy, paternal trisomy 16 is virtually never seen (Hassold *et al.* 1991). It is possible that chromosome 16 is imprinted such that paternally derived trisomy 16 is incompatible with even early embryonic development.

It is not possible to determine whether the non-disjunction events occurred at the first or second meiotic division from the analysis of only one probe on each chromosome, because of the likelihood of recombination events.

We have demonstrated that molecular biology techniques will identify trisomy where cytogenetic analysis is unavailable. In this particular conception five non-disjunction events had occurred, one in the oocyte and four in the spermatocyte. Such multiple non-disjunction events may be more common than has hitherto been thought, but cells containing such multiple trisomies may not grow in culture as a consequence of the additional load on the mitotic machinery, or selection for cells with a normal karyotype. DNA studies may show that a significant proportion of 'idiopathic' early pregnancy loss is associated with complex chromosomal abnormalities.

## Acknowledgments

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British Journal of Obstetrics and Gynaecology
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# CORRESPONDENCE

## Prenatal microbiological risk factors associated with preterm birth

Dear Sir,

We found the study by McDonald *et al* (1992) interesting and a valuable contribution to our understanding of the aetiology of preterm labour. Bacterial vaginosis has been considered to be important in the aetiology of preterm labour for some time and studies conducted by Saling (1991) have shown that early detection and correction of disturbances in the vaginal flora can reduce the occurrence of early preterm delivery.

The two groups of micro-organisms hypothesized are interesting. The direct production of phospholipase by *Gardnerella vaginalis* and *Ureaplasma urealyticum* would result in a general increase in prostaglandin production ($PGE_2$ and $PGF_{2\alpha}$). The response to the enteropharyngeal organisms, however, would depend on the bacterial toxin composition of the particular organism. Bacterial toxins or lipoteichoic acid have been shown to act on uterine decidua to cause increased formation of cytokines (Casey *et al.* 1989; Romero *et al.* 1989). Cachetin/tumour necrosis factor-α ;TNF-α) is synthesized and secreted by human decidual cells in response to lipoteichoic acid and may also cause an increase in $PGF_{2\alpha}$ production. In addition, in amnion cells in monolayer culture, TNF-α, has been shown to stimulate $PGE_2$ formation (Casey *et al* 1989). Therefore, both $PGF_{2\alpha}$ and $PGE_2$ may be released in response to a bacterial challenge. $PGF_{2\alpha}$ is known primarily to stimulate myometrial activity, whilst the main effect of $PGE_2$ is to change the physical properties of the cervix by an alteration in its composition. Depending on the effect of the infecting organism on the decidua, varying quantities of both $PGF_{2\alpha}$ and $PGE_2$ would be released. Where there is a predominance of $PGF_{2\alpha}$ contractions would be stimulated, but as long as there was no change in the state of the cervix, labour would not progress (Oláh & Gee 1992). This may explain the association of *U. urealyticum* with preterm labour and the lack of an association with preterm delivery (Minkoff *et al.* 1984). However, if the release of $PGE_2$ predominates, then cervical change is possible, and in such cases little myometrial activity is required to effect delivery. Therefore, where cervical change is significant, delivery is inevitable (Oláh & Gee 1992). It is with such cases that an impact will be made in the prevention of preterm delivery if correct identification of at-risk pregnancies can be made.

A more comprehensive understanding of the complex biomolecular events that lead to the formation of the prostaglandins, and their relative production in response to various micro-organisms may lead to a better understanding of the pathophysiology of idiopathic preterm labour and delivery. Further studies on the infective aetiology of idiopathic preterm labour are required.

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Saling E. (1991) Effective measures for prevention of late abortions and early premature births. *J Perinat Med* **19** (supplement 2), 10.

## The implications of introducing the symphyseal-fundal height-measurement. A prospective randomized controlled trial

Dear Sir,

There is a serious weakness in most of the research on symphysis-fundus height measurements and the paper by Lindhard *et al.* (1990) illustrates this very well. How can you test a method's validity if it is not given the opportunity to show its full potential? In this paper only three S-F measurements were taken during the whole pregnancy and in 21% only one or two. With so few measurements it is not worth doing it at all!

The Oxford Clinical Trial Data Base Editor's conclusion regarding this paper was 'It would seem unwise to abandon the use of symphysis fundal height measurement unless a much larger trial likewise suggests that it is unhelpful'.

Galbraith *et al.* (1979) commented 'The clinical prediction of IUGR in . . . low risk patients is heavily dependent on the serial measurement of fundal height in order to demonstrate plateauing or static fetal growth'.

At this hospital SF measurements have been used on every pregnant woman at every antenatal visit since 1976. Our original method was rather rough but, since 1981, we have used the method described by Westin (1977) Since 1984, the method has also been used nationally in all government antenatal clinics.

Perinatal mortality covering about 8000 deliveries at Ramotswa has fallen to a record low level of 18/1000 at a time when the perinatal mortality rate at most district hospitals in Africa is at least 30/1000 and often as much as 60/1000.

What is most noteworthy about these figures is that since 1981, the stillbirth and neonatal death rate had been consistently low although the figure elsewhere is in the region of 2·5 to 3. Of the only two stillbirths which occurred after admission to hospital last year, both showed clear failure of fetal growth on their flat S–F graphs. The problem was not whether the graph indicated fetal growth impairment or not but when was the best moment to intervene? Both babies died *in utero* suddenly and unexpectedly, and we clearly waited far too long.

Those who have never used the graph regularly in woman after woman throughout pregnancy are not in any position to make useful comments on its value, even after elegant research and apparently significant statistics. None of the doctors who have worked here and who have used the graph over the years would ever go back to the blind guesswork of pre-SF days.

One of the commonest objections to using the graph is that it will increase interference and the caesarean section rate. Our section rate for many years was 5% and has never gone above 10%!

But the graph has many other uses; the early diagnosis of twins, the detection of polyhydramnios, the usefulness in estimating fatal size in breech and cephalo-pelvic disproportion and the indication of fetal abnormality as in anencephaly when S–F height measurement and dates seem to be inconsistent. Also, the estimation of gestation when dates are not known or are clearly wrong, these problems are our daily bread and butter.

What seems most to deter Western obstetricians from using the SF graph is the ready availability of high-tech methods for assessing fetal well-being. It must be remembered that most of the world's women are not looked after by obstetric teams with all the latest aids to hand, but are, if they are lucky, looked after by general doctors and midwives, who may have little or no interest or experience in obstetrics. If these doctors come out to Africa thinking that without high-tech machines there is nothing they can do to assess pregnant women, how can we ever reduce the appalling statistics?

They need every assistance in making the best of a bad job and for experts to argue about what are significant statistics while babies are dying in thousands is contributing nothing to solving Third World problems. Western centres of excellence have as great a responsibility to mothers in the Third World as they have to their own patients.

Failure to use the partogram is another example. The partogram is still not being used everywhere in the Third World because of the 'we can take it or leave it' attitude of obstetricians in the West. The Third World will only follow if they lead. What you have to do is imagine yourself in a rural centre with only your eyes, ears and hands to help you and see what you make of your patient's condition then! We desperately need you to give the lead. Please don't let us down.

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## Platelets in pregnancy induced hypertension

Dear Sir,

With great interest we read the important article by Louden *et al.* (1991) in which they demonstrated a decreased platelet reactivity in women with pre-eclampsia. In the context of platelet activation in pre-eclampsia, the authors interpreted their observations as reflecting platelet exhaustion. This cross-sectional study performed with the most appropriate methods is very impressing, however, to our estimation the interpretation of changes associated with platelets in pregnancy hypertension need to be explained.

At recent knowledge platelet-activating factor (PAF) has an important role in the female genital tract during human reproduction, including ovulation, fertilization, implantation, embryo development and initiation of parturition (Harper 1989). An increased consumption of platelets, resulting in a mild, transient thrombocytopenia in the mother was observed as a first maternal response to pregnancy (O'Neill *et al.* 1985). Most investigators agree that low grade chronic intravascular coagulation within the utero-placental circulation is part of the physiological response of all women to pregnancy (Letsky 1991). Wallenburg (1987) has suggested that activated platelets are involved in the pathogenesis of pre-eclampsia.

The reports indicate, that there are many problems in the view of consideration and explanation associated with platelets in pregnancy. We therefore propose the following schematic explanation. The controlled activation of platelets is required in physiological pregnancy because of implantation, placental development, maintenance of placental blood flow, induction of labour, etc. In pregnancy-induced hypertension and pre-eclampsia there is a controlled hyperactivation of platelets (controlled by other regulatory mechanisms and by therapy). This hyperactivation of platelets, at least in part, may be physiological and contributes to the maintenance of placental blood supply, but has some pathophysiological consequences (e.g. high blood pressure, increased coagulability). In HELLP syndrome there is an uncontrolled hyperactivation of platelets with concomitant haemolysis, elevated liver enzymes and low platelet count.

Using our terminology, the results of Louden *et al.* (1991) can be explained as the low reactivity of platelets is the consequence of their hyperfunction in pre-eclampsia, furthermore platelet exhaustion is the well documented sign of their hyperfunction.

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## Transvaginal sonography for fetal measurement in early pregnancy

Dear Sir,

I read the report by Kustermann *et al.* (1992) with considerable interest as I have also been collecting data in the first trimester of pregnancy relating fetal size to gestational age. However, there are errors in the regression equations given in their report in Figs. 4 and 5. Inspection of the scatter plots shows that both equations should be simple linear rather than quadratic equations (the regression variables have been squared in error in both cases). Having taken this into account my data are similar to Kustermann's data as they show that crown rump length and abdominal circumference growth are best described by a quadratic regression equation, whereas biparietal diameter (BPD) and head circumference (HC) growth are adequately described by a simple linear equation. There are, however, differences between our data, particularly with respect to the growth of the fetal head. My data show a lower intercept value but a slightly faster rate of growth for both the BPD and HC related to duration of pregnancy in days ($BPD = -24{\cdot}362 + 0{\cdot}533x$; $HC = -81{\cdot}0 + 1{\cdot}80x$). Using the equations to predict values for 16 weeks shows that values derived from my equations are closer to accepted published figures (Fetal Measurement Working Party Report 1990). Differences between our data may be related to the different populations studied (Bristol, UK as opposed to Milan, Italy) or the fact that all patients in my studies had precisely defined dates of conception. Kustermann *et al.* (1992) relied on menstrual data in women with regular cycles (24–26 days) who were certain of the first day of their last menstrual period. Even in women with reported regular 28 day cycles, great variation in cycle lengths are well documented (Arey 1939) and conception dates are generally skewed towards the second part of the cycle (Geirsson 1991).

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## References

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## Author's reply

Dear Sir,

We wish to thank Dr Mills for his interest in our study. He is absolutely right on the two equations of Figs. 4 and 5. They are clearly a printing mistake.

Regarding the other point raised that dates of conception are more reliable than last menstrual period in assessing gestational age, Dr Mills is again correct. Our study included 270 women with regular cycle (24–32 and not 24–26 days as stated by Dr Mills) which is just sufficient to allow meaningful conclusions from a tranverse series. We congratulate Dr Mills for having succeeded in recruiting enough women with certain dates of conception to construct a reference range. This proved practically impossible in our population and indeed it is not common to be sure of conception when evaluating any given group of patients who did not undergo infertility treatment.

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# BOOK REVIEWS

**Lasers in Gynaecology** (Volume 4 in the series Lasers in Medicine) Edited by Chris Sutton, Chapman & Hall Medical, London, New York, 1991, 274 pages, with figures and tables, £40.00

Lasers are expensive and very specialized. Many, if not most, gynaecologists manage their practices without ever needing to use one. Furthermore with an expansion in the numbers of differing types of lasers—initially the $CO_2$, but now also the KTP, Argon, YAG and others—very few practitioners are going to have experience with more than one or two of these devices. Thus Lasers in Gynaecology, edited by Chris Sutton will be, for most of us, nothing more than a window onto a high tech world beyond our ambition or imagination.

Perhaps recognizing this limitation the book has expanded its remit beyond purely laser surgery. Discussion and comparison with other technologies appears frequently in the chapters and general advice on infertility and endoscopic surgery is amply provided.

An introductory chapter on laser physics and tissue interactions is surprisingly clear and understandable, with some very practical advice for the laser surgeon.

Thereafter the applications of the various lasers are reviewed with respect to both laparotomy and laparoscopy. The emphasis is on tubal surgery, adhesiolysis and endometriosis. Because of the common interest of some of the authors and of the similar applications for different lasers, there is a fair amount of repetition in some of the chapters. Even so it is useful to observe the consistency of views expressed and to note that in general no one makes excessive claims for the superiority of lasers over other approaches. The overall view is that laser surgery complements medical or other surgical approaches to gynaecological disease.

There are also chapters on endometrial ablation, laser treatment of CIN and of VIN. These review the better established laser procedures and complete the spectrum of laser applications in gynaecology. It was disappointing to note that the section on laser ablation by the father of the technique provided no new data since previous publications.

The two chapters on the treatment of intra-epithelial neoplasia are excellent reviews of the overall management of these conditions with a rational appraisal of the role of the $CO_2$ laser in their management The inclusion of these chapters significantly widens the appeal of the book. So that with sections on the laparoscopic management of ectopic pregnancy, the complications of endoscopic surgery, photodynamic therapy and future developments it makes a claim to be an essential reference source for any surgeon using a laser or the trainee gynaecologist aspiring to understand an increasingly complex speciality.

**J. A. Davis**

**Physics and Instrumentation of Diagnostic Medical Ultrasound** edited by Peter Fish. John Wiley & Sons, Chichester, 1990, 250 pages, with figures and tables, £15.95

The author states that his goal has been to provide a text that is suitable for students requiring knowledge of the physics and instrumentation to complement and aid study of the clinical use of diagnostic ultrasound, whilst also being a useful introduction for those planning to investigate in greater depth. He has succeeded in these aims.

The book progresses from the basic physics of ultrasound and its propagation through tissue to the instrumentation used in diagnostic imaging. The influence and limitations of transducers on the beam shape for both continuous wave and pulsed wave devices are covered in depth.

Because of the pace of technological advances a book describing instrumentation may soon be out-of-date and useful only as a historical record. The author has managed to avoid this pitfall by showing, with the use of many concise block diagrams, the progression from A-scan devices through to B-scan, real-time scanners, M-mode and finally Doppler instruments.

The sections dealing with the generation of image artefacts and measurement errors should be of particular interest to clinicians. Methods for checking the performance of systems are also described.

No book of this type would be complete without a discussion of the safety aspects of ultrasound. Tissue can be altered or damaged by ultrasound of sufficiently high intensity. The mechanisms which cause physical damage and bioeffects are discussed. The methods for measuring ultrasound power and intensity are introduced and the current recommended safety levels outlined. The author points to some disturbing trends toward higher power instruments which may present potential hazards.

The book is recommended and reasonably priced so that it can be used as a personal reference book.

**Michael C. Carter**

## Books received some of which may be received at a later date

**Gynecologic Oncology Second Edition. Volumes 1 & 2** edited by Malcolm Coppleson, John M. Monaghan, C. Paul Morrow & Martin Tattersall. Churchill Livingstone, Edinburgh, 1992. Volume 1, 728 pages, Volume 11, 731–1497 pages, fully illustrated, £195.00 the set.

**Obstetrics: Normal and Problem Pregnancies** second edition, edited by Steven G. Gabbe, Jennifer R. Niebyl & Joe Leigh Simpson. Churchill Livingstone, New York, Edinburgh, London 1991, 1409 pages, fully illustrated, £65.00.

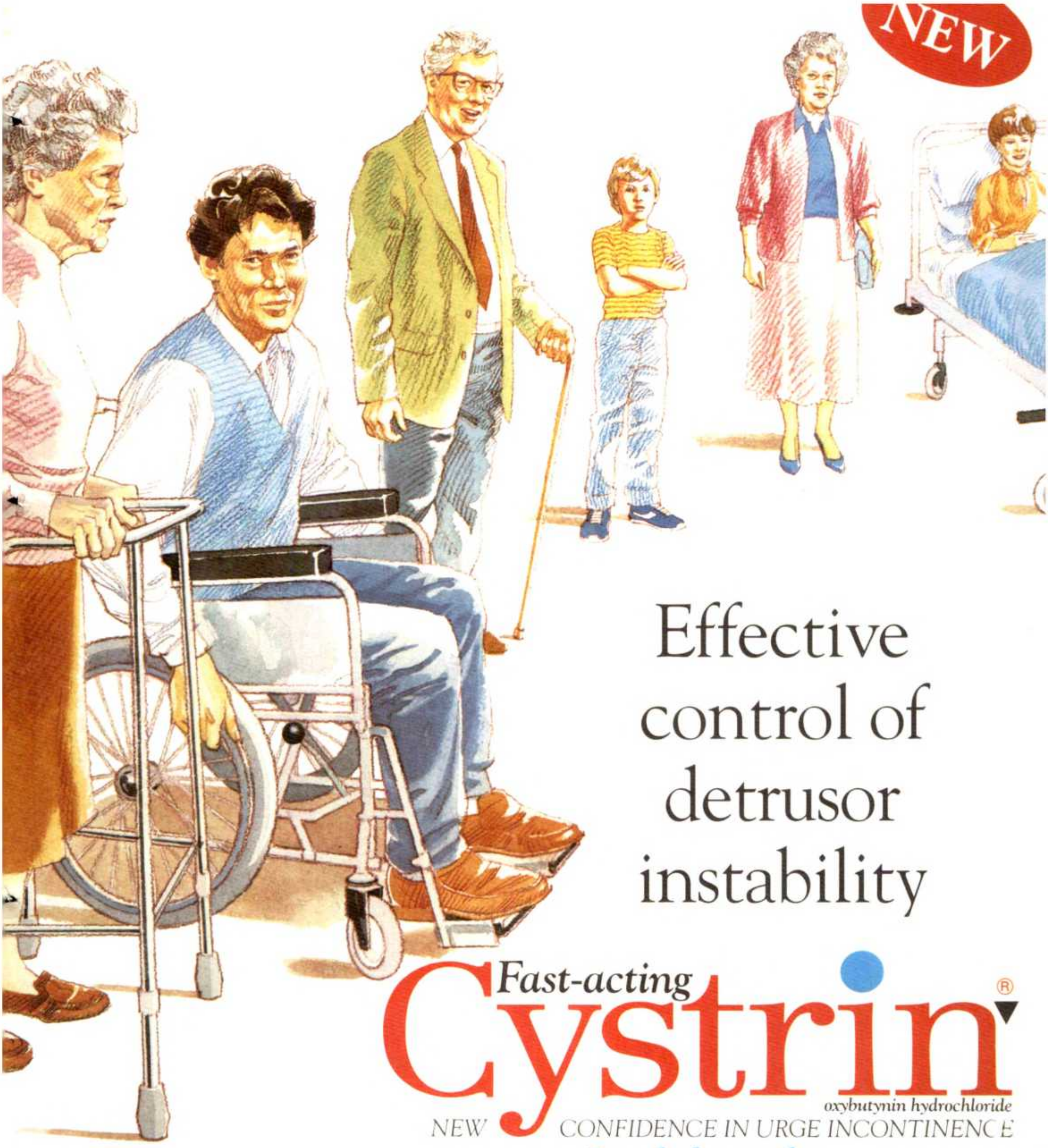
**The Dictionary of Modern Medicine** compiled and edited by J. C. Segen. The Parthenon Publishing Group, Carnforth, Lancs, 1992, 800 pages, illustrated, £48.00.

**Hormone Replacement Therapy** (British Medical Bulletin, Vol 48, No. 2, 1992) edited by K. T. Khaw. Churchill Livingstone, Edinburgh, 249–476 pages, with figures and tables, £43

**Medicine, Patients and the Law**, 2nd edition, by Margaret Brazier. Penguin Books, London, 1992, 495 pages, £9.99

**Clinical Manual of Gynecology** 2nd edition, edited by T. G. Stovall, R. L. Summitt Jr., C. R. B. Beckmann & F. W. Ling. McGraw-Hill Inc., New York, 658 pages, with figures and tables, $29.50

**Medicines: A Guide for Everybody** 7th edition by Peter Parish. Penguin Books, London, 615 pages, £7.99



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# British Journal of Obstetrics and Gynaecology

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Edited by Geoffrey Chamberlain

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# 6 reasons why more doctors prescribe Prempak-C and Premarin than any other HRT.

## 50 YEARS EXPERIENCE

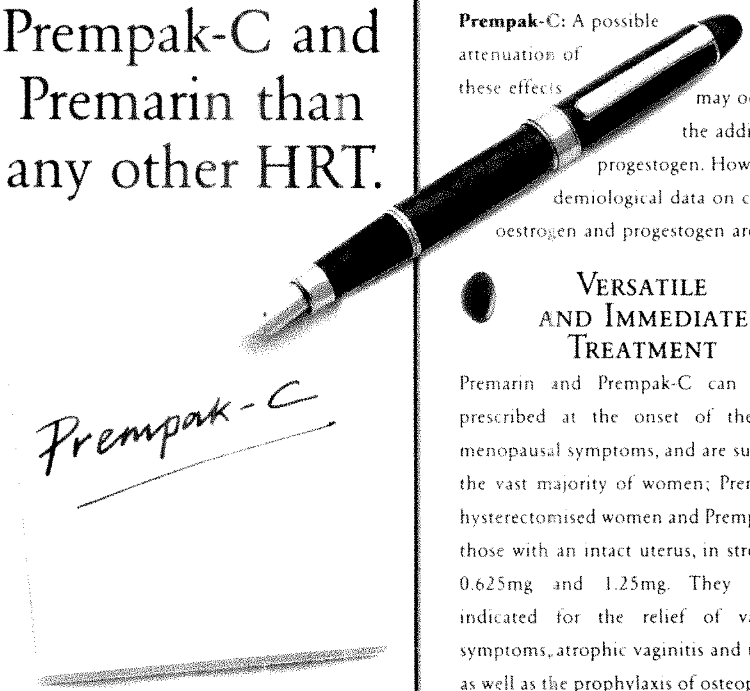
Premarin, a natural conjugated oestrogen, which is also used in the formulation of Prempak-C, is the only oestrogen used in any HRT with 50 years experience. The majority of long term studies, therefore, relate to the conjugated oestrogen found only in these products.

## LONG TERM SAFETY - BREAST CANCER?

Both doctors and patients are justifiably concerned about the potential risks of breast cancer for women taking HRT. Whilst there is suggestive evidence of a small increased risk of breast cancer with long-term HRT (greater than 5 years), this varies with the type and dose of the oestrogen used. However, a recent comprehensive review of 31 studies provides evidence that menopausal therapy consisting of 0.625mg/day of conjugated oestrogens does not increase the risk of breast cancer.[1] Most studies, in fact, relate to conjugated oestrogen and so there is insufficient data to arrive at similar conclusions for any other regimen.

## PROPHYLAXIS OF OSTEOPOROSIS

Prempak-C and Premarin are both indicated for the prophylaxis of osteoporosis in women at risk of developing fractures. A minimum daily dose of 0.625mg Premarin preserves bone mass, therefore reducing the risk of debilitating injuries such as hip fractures, by up to 66%.[2,3] Further estimates suggest that prescribing Premarin for at least 10 years will reduce the risk of mortality linked to osteoporosis by 60%.[4]



## REDUCING CARDIOVASCULAR DISEASE RISKS

**Premarin:** A recent review of considerable epidemiological evidence has shown, overall, a 50% reduction in risk of coronary disease in oestrogen users. The most common form of oestrogen used in all these studies was conjugated oestrogen, i.e. Premarin.

**Prempak-C:** A possible attenuation of these effects may occur with the addition of a progestogen. However, epidemiological data on combined oestrogen and progestogen are limited.

## VERSATILE AND IMMEDIATE TREATMENT

Premarin and Prempak-C can both be prescribed at the onset of the earliest menopausal symptoms, and are suitable for the vast majority of women; Premarin for hysterectomised women and Prempak-C for those with an intact uterus, in strengths of 0.625mg and 1.25mg. They are also indicated for the relief of vasomotor symptoms, atrophic vaginitis and urethritis, as well as the prophylaxis of osteoporosis in women at risk.

## COST EFFECTIVE

Treatment costs are becoming increasingly important, especially as long term therapy can last from 5 to 10 years or longer. Compared to other forms of HRT, Wyeth's products cost remarkably little; Premarin costs just £1.84 and Prempak-C costs £4.06, for 28 days of therapy.[7]

## ABBREVIATED PRESCRIBING INFORMATION

**PREMARIN** **USES:** Menopausal and post menopausal oestrogen therapy in women without a uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures.
**DOSAGE AND ADMINISTRATION:** Natural conjugated oestrogens 0.625mg - 1.25mg daily. Continuous administration is recommended. In women with an intact uterus the addition of a progestogen for 10-12 days per cycle is essential.
**CONTRA-INDICATIONS:** Known or suspected pregnancy and during lactation. History of known or suspected cancer of the breast. Oestrogen dependent neoplasia. Undiagnosed abnormal genital bleeding. Active thrombophlebitis or thromboembolic disorders. Acute or chronic liver disease. Rotor or Dubin-Johnson syndrome. Severe cardiac or renal disease.
**WARNINGS AND PRECAUTIONS:** Some studies have reported a small increased risk of breast cancer in long term oestrogen replacement therapy users (greater than 5 years), others however have not shown this relationship. It is not known whether concurrent progestogen influences this risk. The risk of endometrial hyperplasia and carcinoma with unopposed oestrogen use is lowered by the addition of a progestogen. Diseases that may deteriorate during therapy include otosclerosis, multiple sclerosis, systemic lupus erythematosis, porphyria, melanoma, epilepsy, migraine and asthma. Use with caution in patients with pre-existing uterine fibroids, endometriosis, breast nodules, fibrocystic disease, and in those with a history of deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, cardiac or renal dysfunction. Discontinue if jaundice, migraine, visual disturbances, thromboembolic phenomena or significant hypertension develop. Certain endocrine and liver function tests may be affected. Rarely idiosyncratic hypertension may occur. Discontinue treatment prior to surgery or prolonged immobilisation. Gallbladder disease. Insulin requirements may be altered. Premarin is not an oral contraceptive.
**SIDE EFFECTS:** The following have been reported with oestrogen therapy: premenstrual-like syndrome, increase in size of uterine fibromyomata, vaginal candidiasis, changes in cervical erosion and secretion, cystitis-like syndrome, breast changes, gastrointestinal symptoms, chloasma, melasma, erythema multiforme, erythema nodosum, haemorrhagic eruption, alopecia, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headaches, migraine, dizziness, mental depression, chorea, weight changes, reduced carbohydrate tolerance, aggravation of porphyria, oedema, changes in libido, leg cramps.
**PRODUCT LICENCE NUMBERS:** Premarin 0.625mg PL0011/0165 Premarin 1.25mg PL0011/0166 Premarin 2.5mg PL0011/0167. **BASIC NHS PRICE:** Premarin 0.625mg £1.84 (28 days). For full prescribing information please refer to data sheet.

**PREMPAK-C** **USES:** Menopausal and postmenopausal oestrogen therapy for women with an intact uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures.
**DOSAGE AND ADMINISTRATION:** Natural conjugated oestrogens 0.625mg - 1.25mg daily and one norgestrel 0.15mg tablet should be taken daily from day 17 to day 28 of oestrogen therapy.
**CONTRA-INDICATIONS:** As for Premarin.
**WARNINGS AND PRECAUTIONS:** As for Premarin. Prempak-C is not an oral contraceptive.
**SIDE EFFECTS:** As for Premarin. Breakthrough bleeding and spotting. Change in menstrual flow, dysmenorrhoea, amenorrhoea.
**PRODUCT LICENCE NUMBERS:** Prempak-C 0.625mg PL0011/0161 Prempak-C 1.25mg PL0011/0162.
**BASIC NHS PRICE:** £4.06 - 28 days. For full prescribing information please refer to data sheet.
**REFERENCES** 1 Dupont W D and Page D.L. (1991) Arch. Int. Med. 151, 67-72. 2 Lindsay R. et al. (1984) Obstet. Gynecol. 63, 759-763. 3 Kiel D.P. et al. (1987) NEJM, 317, 1169-1174. 4 Ross R.K. et al. (1989) Lancet, 1, 505. 5 Stampfer M.J. and Colditz G.A. (1991) Prev. Med. 20, 47-63. 6 Stampfer M.J. et al. (1991) NEJM, 325, 756-762. 7 MIMs June 1992.
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**PREMARIN***
**(Conjugated Oestrogens)**

Wyeth Laboratories, Huntercombe Lane South,
Taplow, Maidenhead, Berkshire SL6 0PH.

**PREMPAK-C***
**(Conjugated Oestrogens + Norgestrel)**

# British Journal of Obstetrics and Gynaecology

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(2) The use of confidence intervals is encouraged.
(3) The symbol ± should not be used when presenting SE or SD. Presentation such as 'the mean . . was 14·2 (SD 3·2) mg' is preferred.
(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences.
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Altman, D G., Gore, S M., Gardner, M. J. & Pocock, S J (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493.

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Arrange the list of authors quoted at the end of the text in alphabetical order set out as follows.

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British Journal of Obstetrics and Gynaecology
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COMMENTARY

# Laparoscopic alternatives to laparotomy: a new approach to gynaecological surgery

Two remarkable papers in this issue by the Nezhat brothers (pp. 659 and 664) illustrate what can now be achieved with minimally invasive operative laparoscopy. Boesch (1936) laid the foundation stone for this type of surgery in gynaecology when he described a method of laparoscopic sterilization using tubal coagulation. Power & Barnes (1941) independently developed a similar technique for laparoscopic sterilization in the US and operative laparoscopy became an established gynaecological technique. Early hazards which hindered the widespread adoption of this new form of surgery included tissue burns and air embolism. Development of the 'cold light' source by Fourestier Galdu & Vulmiere and an automatic controlled $CO_2$ insufflation apparatus by Fikentscher & Semm (1959) overcame these difficulties. The first British monograph on this subject was by Steptoe (1967). The instrument's usefulness was increased with the introduction of the Hopkins Rod lens system in 1976 which improved the angle of vision, the depth of field and the clarity of image provided by laparoscopes. These technical improvements greatly increased the convenience and ease of laparoscopy and its use gradually spread until almost all gynaecological departments now have facilities for diagnostic and limited operative laparoscopic surgery.

For most gynaecologists in the UK the matter, for the moment, rests there. Those with a major interest in infertility will have developed Steptoe's techniques for egg retrieval but most UK gynaecologists are content to use the laparoscope only for the investigation of infertility and pelvic pain and as a convenient method of female sterilization. In continental Europe and North America, however, there have been dramatic advances in laparoscopic techniques which greatly increase the scope and potential for this 'minimally invasive' surgical approach.

The main reason for the development of this type of surgery is the recognition that post operative pain, complications and recovery times are related almost exclusively to the size and position of the initial surgical incision. Large classical laparotomy scars are painful and require powerful analgesic medication. The medication and the pain reduce mobility and increase the dependency time so that most patients require around 7 days in hospital to recover from an abdominal wound irrespective of what procedure has been performed beneath the scar. Similarly, post operative convalescent time, which in the UK appears to be between 6 and 12 weeks after major gynaecological surgery, is directly associated with the length of the incision. After laparoscopic surgery associated with small incisions, the post operative recovery period is short and the patient is usually fit to return home within 24–48 h of the procedure, irrespective of the duration of the operation or the nature of the pathology. The possibility of such early recovery was first demonstrated to the author by a surgical colleague who took some 4 h to remove an acutely inflamed gall-bladder laparoscopically, but, in spite of the duration of the procedure and the severity of the pathology, the patient was pain free and fit to go home within 48 h. Gynaecologists are now finding that patients who have had laparoscopically assisted hysterectomy and similar major endoscopic procedures are also able to leave hospital in 1 to 2 days.

To perform any endoscopic surgery safely it is most important to obtain and maintain excellent vision at all times. A rigid 5 mm or 10 mm rod-lens laparoscope appears to be the most satisfactory instrument currently available. This must be used in association with an appropriate high power light source and wide diameter fibreoptic or liquid light cable. I believe that a good quality video camera system is essential not only for the comfort and convenience of the operator but also because it permits other staff to assist the operator and in more complex procedure such assistance is essential. Such a video system is also an indispensable teaching aid. A good $CO_2$ pneumatoperitoneum must be maintained at all times and as several operating ports are used and instruments are frequently removed and re-introduced, loss of gas during the procedure is inevitable. An electronic automatic infusion system which can control both the intra abdominal pressure and the $CO_2$ flow rate is essential. As large quantities of $CO_2$ can be used during a procedure, a system with a large gas reservoir and a fast flow rate is helpful. A facility to recirculate the gas through a filter to remove smoke particles is also of value.

In all these operations it may be necessary to divide or excise tissue. This can be done with conventional heavy and fine scissors modified for use down laparoscopic cannulae. Tissues may also be divided and separated with diathermy blades and beam or fibre lasers. A $CO_2$ laser beam cuts precisely and accurately and is often useful. However, the articulated mirror systems required to direct the laser to the tissue are cumbersome and the $CO_2$ laser wavelength has little haemostatic action so, like conventional scissors, it may be associated with small-vessel bleeding. The fibre lasers such as the KTP, Argon, and particularly the Nd-YAG laser, used with a shaped sapphire tip, cut and coagulate simultaneously and can divide many tissues without bleeding. An ever increasing range of grasping forceps is available. These can improve access to, and visibility of, the pelvic structures. They are inserted down accessory channels which may be placed either side of the midline above the symphysis pubis.

It is particularly important in laparoscopic surgery, as in open surgery, to have available several different techniques to

Correspondence: Dr Ray Garry.

arrest bleeding and produce haemostasis. Monopolar diathermy can be used but unexpected burns have been described, especially when older electrical equipment is used. Bipolar diathermy is safer and is recommended as a method for haemostasis but is not suitable for cutting. A third electrical method devised by Semm (1976) is that of endocoagulation. The endocoagulator tip is heated to 100°C and coagulates tissue proteins. It is an effective and a safe haemostat as it avoids contact between electrical current and the body. Laser energy, particularly the Nd-YAG laser, when correctly applied can arrest bleeding from all but major blood vessels. Considerable interest is now being generated in the haemostatic properties of the Argon Beam Coagulator which has been modified recently for laparoscopic use. Haemostasis may also be obtained in a more conventional manner with preformed Roeder loops which are commercially available. These can be placed around a bleeding pedicle and the slip-knot tightened to secure haemostasis. Individual haemostatic titanium clips can be applied to major vessels to arrest major bleeding. The most recent addition to the range of haemostatic equipment is an automatic stapling device which can be inserted down a 12 mm cannula to place two triple-staged lines of titanium clips simultaneously with an inbuilt knife to cut the tissue between the lines of staples (Multi-Fire Endo GIA 30, AutoSuture UK). In addition to various techniques for the arrest of bleeding it is also essential to have an effective aspiration system to remove blood, contents of ovarian cysts, and peritoneal and irrigation fluid. The treated areas of the pelvis also need frequent cleansing and an appropriate pressurized irrigation system is required.

It is essential that these procedures are not attempted before the operator has access to, and is fully familiar with, such equipment. With the correct use of this equipment, however, it is now possible to perform laparoscopically almost any intrapelvic operation that is currently performed by an open laparotomy procedure. That such minimally invasive procedures are technically possible does not mean that they are always desirable or the best option. Each procedure must be carefully assessed, but for at least some pathologies there is now persuasive evidence that the laparoscopic method is to be preferred. Certainly it is difficult to continue to recommend open laparotomy as a treatment for ectopic pregnancy when laparoscopic salpingostomy and salpingectomy have proved to be so effective in several large series from Europe (Pouly *et al* 1986; Donnez & Nisolle 1989; Dubuisson *et al.* 1990; Kerkstein *et al.* 1990) from the US (Reich *et al.* 1987; DeCherney & Diamond 1987; Loffer 1987) and the UK (Baumann *et al.* 1991). The last group of authors reported that patients who have had an ectopic pregnancy treated laparoscopically remained in hospital for a mean of 1·7 days compared with 5·2 days following open surgery. After laparoscopic treatment, patients returned to work in 2·5 weeks compared with 5·7 weeks after laparotomy. In economic terms laparoscopic treatment was associated with a reduction in hospital costs of 69%, drug costs of 52% and statutory sickness benefits of 50% per ectopic pregnancy. A similar study from the US (Levine 1985) showed an overall hospital cost saving of 49%. If the clinical outcomes are comparable, why continue to use a more painful and disfiguring procedure which cost the patient, her family, the hospital services and the state more money and which more than doubles her recovery time?

The case for the laparoscopic treatment of pain associated with mild and moderate endometriosis is perhaps even more persuasive. This condition is almost invariably diagnosed only at laparoscopy. There is evidence that laparoscopic laser ablation of the endometriotic deposits with $CO_2$ (Davis 1986; Nezhat *et al* 1989; Feste 1990; Sutton & Hill 1990), Nd-YAG (Lomano 1987; Corson *et al.* 1989; Shirk 1989), Argon (Keye & McArthur 1990) and KTP lasers (Daniell 1990) are all effective in relieving the pain of endometriosis in 60–70% of cases. This treatment avoids the need for prolonged course of powerful hormonal medication and appears to be at least as effective as medical management or extensive open abdominal surgery. As the treatment can be given simultaneously with the diagnostic procedure it is virtually free of additional costs and complications. The case for the laparoscopic treatment of endometriomata and extensive endometriosis is less clear cut but is technically quite possible and often beneficial (Donnez *et al.* 1989a; Daniell *et al.* 1991). Extensive rectovaginal and rectosimoid endometriosis is notoriously difficult to treat and it is unlikely that better results could be obtained with open laparotomy than have been reported in this issue of the Journal by Nezhat *et al* (p 664) using a laparoscopic approach.

Benign ovarian cysts can be drained (Burmucic *et al.* 1983), fenestrated (Larsen *et al.* 1986), enucleated with laparosopic dissection (Semm & O'Neill-Freys 1989) or the capsule can be ablated with a laser (Donnez *et al* 1989*b*). Complete oophorectomy, with morcellation of the excised ovary can be performed laparoscopically (Semm & Mettler 1980), and if there is concern about spilling the cysts contents, the ovary can be placed inside a suitable plastic bag before manipulation. Pelvic and abdominally adhesions can be divided readily with conventional (Semm & O'Neil-Freys 1989) or laser modalities (Donnez *et al.* 1989*b*; Daniell 1989) and tubal surgery can be performed in a totally sterile environment with the ultimate in no handling technique with pregnancy rates as good as those obtained with open microsurgical methods (Leventhal 1989).

The surgical treatment of central pelvic pain is more controversial but there is little doubt that if such an approach is considered appropriate then laparoscopic ablation of the uterosacral nerves is technically easy and appears to be effective in about 66% (Daniell 1989; Sutton 1989). Laparoscopic division of the presacral plexus is technically more demanding but as described in this issue by Nezhat & Nezhat (p 659) it is a clinically rewarding procedure producing relief of symptoms in 49 of 52 patients followed up for more than 1 year.

Even more controversial, and perhaps even more challenging, is the operation of laparoscopic hysterectomy. There are now reports of total hysterectomies being performed laparoscopically by a variety of different techniques (Reich *et al.* 1989; Nezhat *et al.* 1990; Mage *et al.* 1990; Magos *et al.* 1991; Semm 1991). These procedures may seem to many no more than a surgical tour de force with little practical relevance at this time. Some of the techniques may take much longer to perform than a standard hysterectomy and some use expensive technology, but the aim of these techniques is to reduce trauma to the tissues and minimize recovery time. The procedure of laparoscopically assisted vaginal hysterectomy involves the division of the anterior leaf of the broad ligament, the reflection down of the bladder and the easy mobilization and removal of the tubes, ovaries and uterine artery pedicles laparoscopically, followed by a very simple securing of the uterosacral and cardinal ligaments in a standard vaginal hysterectomy manner. Patients I have managed in such a manner appeared to recover from the procedure as if they had had a laparoscopy rather than a hysterectomy and were usually fit to leave hospital within 48 h of surgery.

This procedure may have great potential when oophorectomy is appropriate and an early recovery and short convalescence are required or it is necessary to avoid an abdominal scar.

Perhaps even more remarkable is the technique of laparoscopic pelvic lymphandenectomy described by Querleu *et al.* (1991). The excellence of the magnified view allows satisfactory and usually blood free dissection. In a series of 37 cases no major complications were encountered and a mean of 8·7 nodes was removed from each patient to permit accurate preoperative staging of cervical cancer in all cases. Could this ultimately be a forerunner of laparoscopic radical hysterectomy?

Some of these laparoscopic procedures have been described only recently. Most have only been attempted by a relatively small band of skilled enthusiasts, and almost none have yet been exposed to the rigours of randomized clinical trials. Clinical caution is therefore very necessary in such circumstances. All these techniques are, however, now possible, and all offer the exciting options of reduced pain, reduced morbidity, reduced hospital and convalescent time and reduced costs. When combined with the already established colposcopic techniques for the treatment of the cervix and lower genital tract and the equally new hysteroscopic treatments of endometrial pathology, it is clear that now every portion of the female genital tract can be observed and treated with a 'minimally invasive' procedure. If all these procedures are validated then operative gynaecology may well become an almost exclusively endoscopic discipline within a few years.

The down side of the situation is that these are very new procedures, requiring new equipment and skills. No gynaecologist irrespective of seniority and proficiency at open surgical techniques can assume that they can take up this new approach without extensive retraining and study. The procedures cannot be done 'on the cheap'. Much expensive equipment is required. Every member of the gynaecological team needs a fresh approach. Theatre staff have completely different roles caring for lasers, video monitors and the whole range of specialized laparoscopic equipment. More operating time may be required but considerably fewer inpatient beds may be needed. Traditional teaching ward rounds cannot take place because most of the patients are in and out on the same day, and this presents significant implications for nursing, undergraduate, and postgraduate medical education. The rapid throughput of patients puts new and additional strains on the secretarial services and the support services. New pre-admission clinics are needed to cope with the large number of short stay cases and this also involves significant changes in working practices for our anaesthetic colleagues.

The implications for this new approach are little short of revolutionary for the future practice of operative gynaecology. These changes do not affect just a small group of our speciality but are of importance to every practising gynaecologist. It is vital that before these procedures are widely adopted each must be carefully assessed and validated individually. It is also of the utmost importance that each gynaecologist and all the associated team are properly trained and 'accredited' for these new techniques. To minimize the risk of adverse outcomes and to maximize the potential benefits of each new procedure, every endoscopic unit must be adequately equipped and funded. Managers, politicians and patients must be advised that the potential benefits will only be realized if sufficient attention is given to providing adequate levels of funding, equipment and training. Above all, these new procedures should only be introduced, as the Nezhat brothers advise, gradually so that gynaecological endoscopic surgery can be effective, safe and without unnecessary complications.

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OBSTETRICS

# Survival time after AIDS in pregnancy

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**ABSTRACT**

**Objective** To examine the suggestion, based on theoretical considerations and case reports, that pregnancy decreases survival time after AIDS (acquired immunodeficiency syndrome).

**Design** A total population study in Edinburgh.

**Setting** A city with a moderately high prevalence of human immunodeficiency virus (HIV) infection in women.

**Subjects** AIDS has been diagnosed in 22 women, five of whom had a pregnancy.

**Main outcome measures** Clinical characteristics, disease presentation, lymphocyte markers, pregnancy outcome, subsequent progress and survival time.

**Results** Pregnancy was not obviously associated with a difference in clinical findings. The mean survival time for the three women with a pregnancy who died was 24 months and for the 11 women without a pregnancy it was 15 months. ($P = 0{\cdot}63$ log rank test).

**Conclusions** The clinical presentation, severity of the illness and laboratory findings were not obviously different in pregnancy. All three women who had *Pneumocystis carinii* pneumonia for the first time in pregnancy survived this initial episode. Survival time was not obviously reduced by the conjunction of pregnancy with AIDS.

Whether or not pregnancy has an adverse effect on the course of human immunodeficiency virus (HIV) infection remains uncertain. Most attention has been paid to deterioration in prognostic markers (MacCallum *et al.* 1989; Biggar *et al.* 1989) and from the available information it seems unlikely that pregnancy has a major adverse effect on asymptomatic women. However, there are other possible ways in which pregnancy could affect HIV disease. In susceptible, immunocompromized women the additional pregnancy-induced fall in $CD_4$ lymphocyte count (Sridama *et al.* 1982; Castilla *et al.* 1989) could precipitate major disease; the fatality rate of AIDS (acquired immunodeficiency syndrome) could be higher in pregnancy; and even if there is recovery from major disease, pregnancy could result in poorer subsequent prognosis. As discussed below, there are theoretical reasons why all of these possibilities could apply, and there are supporting case reports. However, there are no population derived data.

We studied all women in Edinburgh who had a diagnosis of AIDS to examine the effect of pregnancy. We aimed to study survival time after *Pneumocystis carinii* pneumonia (PCP) in particular, as this is the most common AIDS defining event in women (Fleming *et al.* 1991) and other conditions are associated with significantly different survival times (Patris *et al.* 1991).

## Subjects and methods

A data base for pregnancy has been created from a number of sources (Johnstone *et al.* 1989). This allows study of all HIV infected women, with appropriate drug using and neighbourhood controls, on a total population basis. Up to 31 October 1991 there had been 173 pregnancies (90 deliveries) in HIV infected women. This population is remarkably homogeneous in terms of ethnic group, home address and socio-economic group. Most are Scots women living in areas of high deprivation index under adverse socio-economic conditions (Johnstone *et al.* 1992). Nearly 80% had a history of injection drug use and nearly 20% had a sexual partner who was known to be HIV seropositive through injection drug use. This population is relatively static, therefore long term follow up is possible for a high proportion of women.

There is a centralized service for hospital based infectious disease management at the City Hospital, Edinburgh, and the data base for this service includes Centre for Disease Control (CDC) staging, entered at each outpatient visit or hospital admission.

Using these two data bases, we examined the notes of all women with a diagnosis of AIDS and we recorded details of the AIDS defining illness and subsequent progress. All AIDS notifications of women in Edinburgh were also checked to ensure that ascertainment was complete: there were no further cases.

There were 315 known HIV seropositive Edinburgh women tested in Lothian laboratories up to 31 May, 1991 (Communicable Diseases [Scotland] Unit statistics). The first observed seroconversions in drug users occurred in 1983 with most women becoming infected between 1984 and 1985. It is therefore only in recent years that AIDS in women has been seen, with a large increase anticipated over the next few years. Survival time was examined statistically using a log rank test.

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Table 1. Characteristics of five women with AIDS during pregnancy

| Age* (years) | Gestation at diagnosis of AIDS (weeks) | AIDS defining diagnosis | Leading symptoms | Duration of symptoms (weeks) | $CD_4$ lymphocyte count (ratio $CD_4/CD_8$) | Diagnosis | Pregnancy outcome | Subsequent progress | Survival time from AIDS diagnosis (months) |
|---|---|---|---|---|---|---|---|---|---|
| 21–25 | 14 | PCP | Severe dyspnoea, dry cough | 2 | 50<br>0·1 | Open lung biopsy | Termination at 18 weeks | Cerebral toxoplasmosis, CMV, died of bronchopneumonia | 20 |
| 26–30 | 35 | PCP | Dyspnoea, dry cough,<br>weight loss | 2<br>8 | 38<br>0·4 | Presumptive | Term delivery | Cerebral toxoplasmosis, died of cerebral toxoplasmosis | 23 |
| 31–35 | 1 week post partum | PCP | Dyspnoea, exhaustion | 8 | 169<br>0·6 | Induced sputum | Term delivery | Alive | Alive |
| 21–25 | 3 months before pregnancy | PCP | Dyspnoea | 3 | 60<br>0·3 | Bronchoscopy | Termination at 8 weeks | CMV retinitis, died of renal failure, adult RDS | 29 |
| 21–25 | 14 months before pregnancy | PCP | Dyspnoea | 4 | 50<br>0·3 | Induced sputum | Termination at 8 weeks | Cryptospondiosis | Alive |

*Mean 25 years, median 27 years.

PCP = *Pneumocystis carinii* pneumonia; CMV = cytomegalovirus: RDS = respiratory distress syndrome.

## Results

Twenty two women had a diagnosis of AIDS made in Edinburgh by October 1991. The AIDS defining diagnoses were: *Pneumocystis carinii* pneumonia in 16, oesophageal candidiasis in four and cytomegalovirus (CMV) retinitis in two (one in conjunction with cerebral toxoplasmosis). The presumed routes of infection were: injection drug use in 16, sex with an infected drug user in five and no known infected partner in one.

Five women, all with pneumocystic pneumonia, were pregnant (Table 1). In three women the initial episode occurred during pregnancy. The remaining women had the condition first diagnosed 3 months and 14 months before becoming pregnant. Three women accepted termination of pregnancy on strong medical advice, the other two were delivered at term. The women all presented with dyspnoea, particularly on exertion and often marked, together with either a cough, weight loss or exhaustion. The symptoms had been present for weeks or months. Oxygen saturation or $PaO_2$ were grossly abnormal in three women, and chest X-rays were abnormal in three. All five women were treated with high dose co-trimoxazole, and two were treated with pentamidine in addition.

Data relating to women who did not have a pregnancy after a diagnosis of AIDS are shown in Table 2. The age and $CD_4$ lymphocyte ranges are similar to the women who had a pregnancy. Women with pneumocystic pneumonia all presented with dyspnoea together with a cough, weight loss, lassitude or cyanosis. Seven of nine had a $PaO_2 < 10$ kPa and seven of 11 had abnormal chest X-rays.

Only one woman in the series died at the initial presentation of pneumocystic pneumonia, and she was not pregnant. Survival time in the women with a pregnancy was within the range for the whole group. The mean survival time for the three women with a pregnancy who died was 24 months and for the 11 non-pregnant women it was 15 months ($P = 0·63$, log rank test).

## Discussion

We share the general concern about progression of HIV disease during pregnancy, fuelled by the apparently worse prognosis of a number of infectious diseases in pregnancy (Weinberg 1984; Brabin 1985), the alteration and possible impairment of cell mediated immunity in normal pregnancy (Sridama *et al.* 1982; Castilla *et al.* 1989; Weinberg 1987) and anecdotal reports of clinical deterioration and mortality in HIV disease in pregnancy (Jensen *et al.* 1984; Antoine *et al.* 1986;

Table 2. Characteristics of 17 women with AIDS and no pregnancy at or after diagnosis

| AIDS defining diagnosis | Number of women | Age (years) | | $CD_4$ lymphocyte count | | Progress | | Survival time since diagnosis of AIDS (months) |
|---|---|---|---|---|---|---|---|---|
| PCP | 11 | Range | 21–34 | Range | 5–180 | Lost to follow up | 1 | — |
| | | Mean | 28 | Mean | 68 | Alive | 4 | 3, 7, 13, 15 |
| | | Median | 28 | Median | 40 | Dead | 6 | 1 (week), 5, 10, 18, 29, 46 |
| Other | 6 | Range | 21–33 | Range | 5–160 | Alive | 1 | 4 |
| | | Mean | 28 | Mean | 69 | | | |
| | | Median | 28 | Median | 60 | Dead | 5 | 4, 5, 6, 16, 29 |

PCP = *Pneumocystis carinii* pneumonia.

Minkoff *et al.* 1986; Wetli *et al.* 1983; Koonin *et al.* 1989; Joncas *et al.* 1983; La Pointe *et al.* 1985; Kell *et al.* 1991).

The risk of developing opportunistic infections has been related to a number of prognostic markers including the absolute number of $CD_4$ lymphocytes (Fernandez-Cruz *et al.* 1990; Schechter *et al.* 1989; Phillips *et al.* 1989). Short term profound immunodepression has been reported and opportunistic infections characteristic of AIDS have developed during or shortly after acute HIV infection (Cooper *et al.* 1988; Cilla *et al.* 1988; Pedersen *et al.* 1987; Tindall *et al.* 1989; Isaksson *et al.* 1988). Therefore a fall in absolute $CD_4$ lymphocyte count associated with pregnancy could, for a short period, increase the risk of an opportunistic infection developing during pregnancy (Biggar *et al.* 1989; Ravizza *et al.* 1990; Chiphangwi *et al.* 1991).

Pregnancy could also increase the probability of an AIDS defining illness being fatal, because of delay in diagnosis (a low index of suspicion, or symptoms of dyspnoea or tiredness falsely ascribed to pregnancy), or because of less aggressive investigation and treatment (concern about the fetus), or because of a genuine difference in clinicopathology due to pregnancy induced alterations in cell mediated immune response. These considerations could also affect longer term prognosis.

Previous case reports have suggested that the outcome of AIDS in pregnancy is poor. In the United States the first five reported cases of pneumocystic pneumonia in pregnancy were fatal (Jensen *et al.* 1984; Antoine *et al.* 1986; Minkoff *et al.* 1986), as was a case of listeria bacteraemia in which AIDS was assumed (Wetli *et al.* 1983). Koonin *et al.* (1989) reported 18 previously unpublished cases of women who had AIDS during pregnancy and who died within a calendar year of culmination of the pregnancy. There were early reports of pregnancy associated deaths from AIDS from Canada (Joncas *et al.* 1983; La Pointe *et al.* 1985). As the disease has become more common, such fatalities probably tend not to be reported, but in the United Kingdom Kell *et al.* (1991) reported one woman who died of PCP when 10 weeks pregnant. In contrast, Hicks *et al.* (1990) recently described a single case who, they claimed, was the first reported pregnant woman with pneumocystic pneumonia to survive. Two other women are known to have survived this infection in pregnancy (Minkoff *et al.* 1990).

This bias towards mortality is unlike the situation in non-pregnant individuals. Mortality in women from first presentation with pneumocystic pneumonia was only around 16% by 1987 (Rothenberg *et al.* 1987) and should now be lower with more effective treatment and better methods of early diagnosis. Although the factors listed above could account for a particularly high case fatality rate in pregnancy, the gloomy outlook may simply represent reporting bias. Physicians are more likely to report fatal cases, editors may be more likely to publish such cases and nothing is known of other, non-fatal, AIDS defining illness in the populations from which these women were drawn.

There is no satisfactory information on survival time after AIDS in pregnancy. Koonin *et al.* (1989) reported a survival time of only 113 days, which is considerably reduced compared with studies of women not recently pregnant (Rothenberg *et al.* 1987), but this is systematically biased by selection of only deaths within one year of pregnancy.

This Edinburgh series describes only 22 women with AIDS, but it is based on a total, well-described geographical population and it provides the only information available on presentation with, and survival time after, AIDS in pregnancy. Some tentative conclusions may be drawn. Firstly, the clinical presentation, severity of the illness and laboratory findings were not obviously different in pregnancy. Secondly, all three women who had pneumocystic pneumonia for the first time in pregnancy survived this initial episode. Finally, survival time was not obviously reduced by the conjunction of AIDS and pregnancy.

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OBSTETRICS

# Experience with the Cardial inferior vena cava filter as prophylaxis against pulmonary embolism in pregnant women with extensive deep venous thrombosis

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**ABSTRACT**

**Objective** To report the use of the Cardial inferior vena caval filter as prophylaxis against pulmonary embolism in pregnant women with extensive iliofemoral thrombosis.

**Setting** Leicester Royal Infirmary.

**Subjects** Four pregnant women with extensive iliofemoral thrombosis, deemed to be at high risk of pulmonary embolism, managed over a period of one year.

**Technique** In addition to standard full anticoagulation with heparin, the Cardial inferior vena cava filter was introduced percutaneously under local anaesthesia through the unaffected contralateral femoral vein and positioned in the inferior cava below the renal veins.

**Results** The procedure was uncomplicated and did not compromise feto-maternal condition. There was no evidence of pulmonary embolism after filter insertion.

**Conclusion** The use of inferior vena cava filters should be considered as an adjunct to intravenous anticoagulation in pregnant women with extensive deep vein thrombosis of the lower limbs.

Thromboembolic disease is the major cause of maternal mortality in the United Kingdom (Department of Health *et al.* 1991) accounting for 22% of all direct maternal deaths in the triennium 1985–1987. Treatment of deep venous thrombosis by anticoagulation alone may not be sufficient to prevent fatal pulmonary embolism (Barritt & Jordan 1960; Messmer & Greenfield 1985; Golueke *et al* 1988). There are a few reports of the use of inferior vena caval (IVC) filters in the prevention of pulmonary embolisation in pregnancy (Scurr *et al.* 1981; Hux *et al.* 1986; Banfield *et al.* 1990; Greenhalgh *et al.* 1990) and these have all concerned the use of the Greenfield IVC filter. We present the case histories of four women, who presented over a period of 1 year (1990–1991), with extensive ilio-femoral thrombosis. Management consisted of placement of a Cardial IVC filter, in addition to standard intravenous anticoagulation.

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## Patients and methods

### *Case 1*

A healthy 26-year-old primigravida booked for antenatal care at 14 weeks gestation in a twin pregnancy. At 23 weeks, absence of fetal movements was reported and an ultrasonic examination revealed intrauterine death of both fetuses. The situation was initially managed conservatively in anticipation of spontaneous labour but 1 week later the patient attended hospital complaining of pain, swelling and discolouration of the left leg. Clinical findings were consistent with a left iliofemoral thrombosis and Doppler ultrasonography revealed absence of flow in the left femoral vein. Intravenous infusion of heparin was started, with the intention of maintaining the partial thromboplastin time at 2–2·5 times the normal. The uterus was irritable at this stage A percutaneous venacavagram was performed under local anaesthesia via the right femoral vein to assess the extent of the thrombus. This revealed filling defects in the left femoral, external iliac and common iliac veins. In addition, the appearance of streaming of contrast around the clot was noted which suggested instability and a high risk of embolization (Scurr *et al.* 1981).

Using local anaesthetic, a Cardial IVC filter (Fig. 1) was inserted via the right femoral vein. Under image intensifier control, an introducing catheter loaded with the filter was positioned below the renal veins in the inferior vena cava and the filter was released. The small recurved hooks at the ends of the limbs of the filter anchored the device to the caval wall. Intravenous heparin therapy was continued after insertion of the filter The patient miscarried shortly afterwards, heparin being discontinued until after the delivery. Heparin therapy was then started again and continued for a further 8 days; warfarin was commenced 72 h later. The pain and swelling of the left leg began to resolve gradually. Doppler ultrasonic examination 4 days after insertion of the filter demonstrated that the device had not migrated, and there appeared to be good flow above and below it. The patient was discharged 11 days after insertion and has been followed up for 9 months. Warfarin was continued for 6 months and oedema of the left leg was slow to settle.

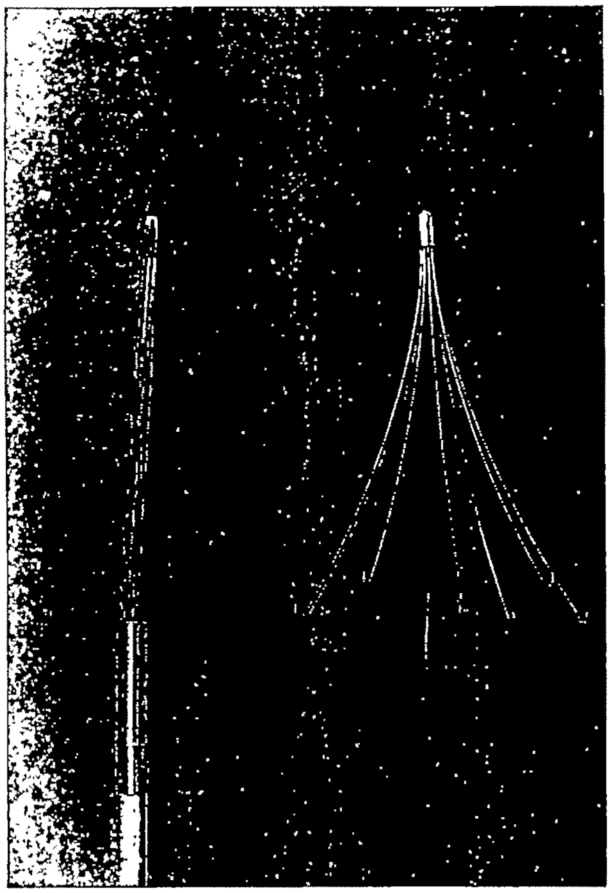

**Fig. 1.** The Cardial filter with the narrow gauge catheter for insertion.

Investigations for systemic lupus erythematosus were negative.

*Case 2*

A 22-year-old healthy primigravida had an uneventful pregnancy until 39 weeks gestation, when she developed left groin pain and swelling of the left leg. Clinical findings were compatible with a diagnosis of left ilio-femoral thrombosis. Venography failed to demonstrate thrombus in the left femoral or calf veins. However, venographic examination of the iliac veins was omitted. Anticoagulation was withheld until 3 days later, when the patient complained of worsening leg pain and increasing swelling. A venacavagram showed extensive left iliofemoral thrombosis (Fig. 2). A Cardial IVC filter was inserted.

Intravenous heparin was continued post operatively until spontaneous labour ensued 13 days later. Analgesia was administered via a patient-controlled analgesia system (PCAS) and prophylactic antibiotics were used to cover labour. Elective ventouse delivery of a healthy male infant, birthweight 4010 g, was carried out. The third stage of labour was managed with intravenous ergometrine and was uncomplicated. Heparin was recommended 30 min post delivery and warfarin was started on the third postnatal day. An abdominal X-ray at this time (Fig. 3) showed that the filter had not migrated from its initial position. The patient was discharged home 10 days

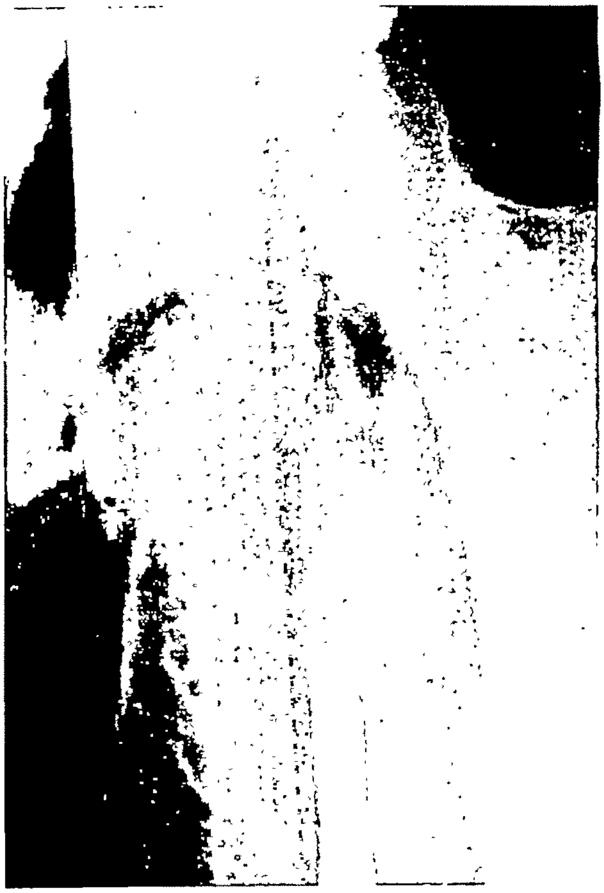

**Fig. 2.** Venacavagram: left iliofemoral filling defect with sharp meniscus of cut-off. Collateral vessels also defined.

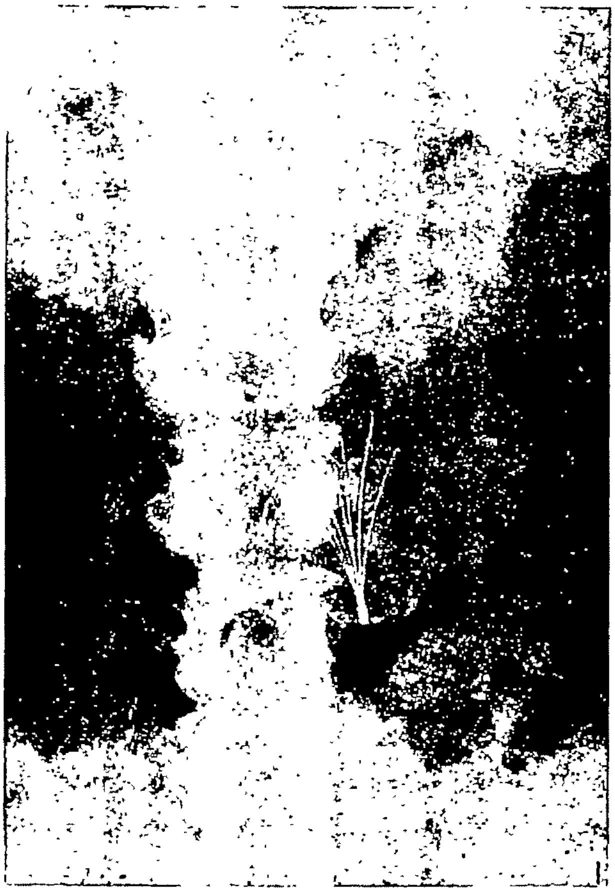

Fig. 3. Abdominal X-ray in the puerperium: filter in correct position in the inferior vena cava.

after delivery, and warfarin was continued for 4 months. At follow-up 4 months after filter insertion, the woman was well with no leg pain or swelling.

*Case 3*

A 25-year-old healthy primigravida had an uneventful pregnancy until 37 weeks gestation when she was referred to hospital with low backache radiating to the posterior aspect of the left thigh. There was no clinical evidence of venous thrombosis. She attended again 3 days later with severe left groin pain which was exacerbated by standing. The left leg appeared normal and there was no differential leg swelling. Nevertheless, the possibility of ilio-femoral thrombosis was considered. Intravenous heparin was administered and Doppler ultrasonography carried out. This confirmed the absence of flow in the left femoral and external iliac veins. A venacavagram was carried out via the right femoral vein. This demonstrated filling defects in the left femoral and iliac veins and at the origin of the inferior vena cava.

A Cardial inferior vena cava filter was introduced and positioned below the renal veins without complication. Intravenous heparin was continued. A healthy male infant weighing 3760 g was born by ventouse at 42 weeks gestation. There were no problems at follow-up at 4 months following filter insertion.

*Case 4*

A 28-year-old primigravida presented at 32 weeks in a previously uncomplicated pregnancy with a 24-h history of swelling of the left leg and a severe left groin pain. There was obvious swelling of the left calf muscles and thigh, with tenderness over the left popliteal fossa, thigh and femoral vessels. Doppler ultrasound confirmed the diagnosis of thrombus in the left femoral vein at the groin and full heparinization was commenced.

A Cardial IVC filter was inserted as described previously without any complication. Intravenous heparinization continues and at the time of writing this patient has not yet delivered.

## Discussion

The incidence of thromboembolic disease in pregnant women is believed to be increasing (Scurr *et al.* 1981) and in particular, the number of deaths from pulmonary embolism occurring antenatally was at its highest in 1985–1987 (DHSS 1991). Although heparin anticoagulation is the standard management of deep venous thrombosis in pregnancy, it is recognized that some patients will develop pulmonary emboli or recurrent deep vein thrombosis despite adequate anticoagulant therapy (Barritt & Jordan 1960; Messmer & Greenfield 1985; Golueke *et al.* 1988). In the non-pregnant population, the use of anticoagulation alone in the management of thromboembolic disease is associated with an 18% rate of recurrent pulmonary emboli (Santos & Lansman 1982), half of these recurrences proving fatal. Where extension of clot into the common iliac veins or low inferior vena cava can be demonstrated, this is believed to indicate a particularly high risk of subsequent pulmonary embolism (Nicolaides 1975).

These observations have prompted physicians to supplement standard anticoagulation regimens with therapies designed to prevent passage of large emboli to the lungs. Direct surgical approaches to the inferior vena cava for ligation and/or embolectomy are technically difficult and are associated with frequently severe maternal and fetal complications (Messmer & Greenfield 1985; Golueke *et al.* 1988; Scurr *et al.* 1981; Banfield *et al.* 1990; Greenhalgh *et al.* 1990). Thrombolytic agents are associated with significant fetal wastage rates (Hall *et al.* 1972). These treatments have been superseded by the insertion of transvenous filters (Messmer & Greenfield 1985; Golueke *et al.* 1988; Gomez *et al.* 1983; McCollum. 1987) which have the ability to trap emboli without significantly reducing flow in the inferior vena cava (Greenfield *et al.* 1977). These filters can be positioned accurately, and migration of the device or perforation of the inferior vena cava have not been reported in pregnant subjects. The patency rate of Greenfield filters is reported as 97% at 2-year follow-up in non-pregnant subjects (Greenfield *et al.* 1977). In addition there appears to be a lower incidence of leg swelling after filter insertion compared with inferior vena cava ligation (Wingerd *et al.* 1978). Recurrence of pulmonary emboli after filter insertion has been reported in only 1–3% of subjects (Bomalaski *et al.* 1982). Despite the open design of IVC filters, emboli larger than 3 mm are successfully trapped (Greenfield *et al.* 1977).

The Cardial IVC filter has a simple delivery system for percutaneous insertion and has the advantage of requiring only a size 12 FG catheter of external diameter 3·5 mm, compared to the Greenfield filter which requires a 24–28 FG catheter of 9 mm external diameter. This reduces local complications at the puncture site whilst increasing the ease of filter insertion.

There has been only one previously reported case of a pregnant woman with extensive ilio-femoral thrombosis managed by insertion of a Greenfield IVC filter as prophylaxis against pulmonary embolism (Scurr *et al.* 1981). There have been isolated case reports of pregnant women with pulmonary emboli who were subsequently managed by insertion of a Greenfield IVC filter to prevent recurrence (Banfield *et al.* 1990; Greenhalgh *et al.* 1990). A series of six pregnant women who had IVC filters inserted because they developed either recurrent embolic disease or other complications while on heparin therapy has been reported (Hux *et al.* 1986).

There has only been one report of filter insertion via the femoral route (Hux *et al.* 1986). In our patients, the filters were inserted percutaneously via the right femoral vein without complication. In particular, the presence of the gravid uterus did not hinder accurate positioning of the filter. Filter insertion via the internal jugular vein is technically more difficult and has been associated with air embolism, cardiac arrythmia, haemopericardium and inadvertent release within the heart (Denny *et al.* 1988).

Radiographic follow-up is essential after placement of IVC filters even in asymptomatic patients to check for evidence of migration, angulation of the device (Messmer & Greenfield 1985; Greenfield *et al.* 1977), or rarely, perforation of the caval wall (Phillips *et al.* 1980). Malalignment may predispose to further thrombosis (McAuley *et al.* 1984). It is recommended that anticoagulation be continued for 3–4 months after filter insertion (McCollum 1987). This is believed to be sufficient time to treat the initial thrombosis and to allow lysis of any clot trapped by the filter.

In clinical practice, IVC filter placement must be regarded as permanent. Within 4 days of filter insertion the legs of the filter are endothelialized, and filter removal is technically impossible after 12 days (Wells 1989). Clearly the filter needs to remain in place beyond this time in order to protect against embolization.

Our experience of the use of the Cardial filter, in addition to standard anticoagulation for patients with extensive ilio femoral thrombosis, indicates that the procedure is safe, has not thus far compromised maternal or fetal well being and has protected against the development of pulmonary embolism. The only recorded long-term complication thus far is persistent leg swelling, which has occurred in one of our four patients. However, larger studies are required before reaching firm conclusions on the safety and efficacy of IVC filters in pregnancy.

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# The effect of magnesium sulphate on blood flow velocity in the maternal retina in mild pre-eclampsia: a preliminary colour flow Doppler study

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**ABSTRACT**

**Objectives** To investigate the use of colour flow Doppler ultrasound to identify retinal blood vessels in women with mild pre-eclampsia and to assess the effects of an infusion of magnesium sulphate on the baseline retinal blood flow-velocity.
**Design** Prospective descriptive study.
**Setting** Ben Taub Hospital, Baylor College of Medicine, Houston, Texas, USA.
**Subjects** Eight women with mild pre-eclampsia
**Interventions** Baseline colour flow Doppler ultrasound assessment of the central retinal artery (CRA) and posterior ciliary artery (PCA) blood flow-velocity before intravenous infusion of 6 g of magnesium sulphate in 100 ml of 5% dextrose water over 20 min, followed by repeat Doppler measurement.
**Main Outcome Measures** Blood pressure, heart rate, pulsatility index (PI), resistance index (RI), angle-corrected flow-velocity (cm/s).
**Results** The CRA and PCA were easily and reliably identified. The infusion of 6 g of magnesium sulphate significantly reduced ($P<0{\cdot}05$) the mean CRA PI from 1·42 (SD 0·67) to 0·93 (SD 0·18) and the mean CRA RI ($P < 0{\cdot}008$) from 0·62 (SD 0·07) to 0·53 (SD 0·10). The PCA PI decreased ($P = 0{\cdot}01$) from 0·97 SD (0·14) to 0·78 SD (0·18) and the PCA RI decreased ($P = 0{\cdot}02$) from 0·58 SD (0·07) to 0·48 SD (0·09). Angle-corrected flow-velocity decreased non-significantly after the magnesium sulphate infusion.
**Conclusions** Patients with pre-eclampsia have high CRA and PCA flow-velocity suggestive of vasospasm. Magnesium sulphate acutely vasodilates the small arteries in the retina, increasing retinal blood flow. Changes in the blood flow in the retina may be indicative of similar changes in other end-arterial branches of the internal carotid artery. This non-invasive Doppler method may provide a means to monitor the effects of therapeutic interventions in patients with pre-eclampsia.

Pre-eclampsia is a major cause of maternal morbidity and mortality. The aetiology is still unclear, but vasospasm, ischaemia and endothelial damage (Musci *et al.* 1988) are thought to be involved in the initiation and propagation of this disease process. Segmental vasospasm of arterioles in the eye has been reported in women with pre-eclampsia, occasionally being so marked as to result in intermittent obstruction to capillary flow (Landesman *et al.* 1954). Visual changes in severe pre-eclampsia have been associated with retinal vasospasm (Jaffe & Schatz 1987), and may represent a global reduction in cerebral blood flow. Colour flow Doppler ultrasound makes it possible to identify and study the blood flow characteristics in specific vessels in the eye (Erickson *et al.* 1989; Lieb *et al.* 1991). Since the central retinal artery and posterior ciliary artery are end-arterial branches of the internal carotid artery, changes in these vessels may reflect changes in other small diameter vessels in the brain. The reproducibility and reliability of colour flow Doppler measurements has been studied by Lieb *et al* (1991) and they found a good correlation between measurements taken on two separate occasions on the same day from a total of 40 patients. The current preliminary study was designed to explore the use of this aspect of colour flow Doppler technology in the assessment of retinal blood velocity indices in pregnancy, and to record the changes in retinal blood flow-velocity characteristics following the administration of a 6 g intravenous dose of magnesium sulphate in women with mild pre-eclampsia.

## Patients and methods

The protocol was approved by the Baylor College of Medicine Institutional Review Board and by the Harris County Review Board. All women gave written, informed consent.

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Women with mild pre-eclampsia scheduled to receive magnesium sulphate as anti-seizure prophylaxis were eligible for inclusion. Women who were in labour or had already received a potentially vasoactive drug were excluded. Essential hypertension, chronic renal disease, seizure disorders, diabetes mellitus, autoimmune disease, and any condition perceived to have an effect on the cerebral or orbital vasculature were also cause for exclusion.

A Quantum 2000 angiodynagraph system (Quantum Medical Systems, Issaquah, Washington) was used for the colour flow Doppler studies. A 7·5 MHz linear phased array transducer with a 0·2 mm x 0·2 mm sample volume was used to image each eye. The estimated in-situ peak temporal average (SPTA) intensity at 4·2 cm depth in the colour imaging mode is 7 mW7cm$^2$ for the 7·5 mHz transducer (data provided by Quantum Medical Systems). During colour flow Doppler spectrum analysis the SPTA intensity is approximately 71 mW/cm$^2$. In this mode the SPTA intensity exceeds the limits suggested by the Food and Drug Administration guidelines of 17 mW/cm$^2$ for opthalmic application, but is still within the safety limits set by the American Institute for Ultrasound in Medicine (Lizzi & Mortimer 1988). Spectrum analysis was limited to approximately 1 min in each eye, and the total examination was limited to approximately 5 min for each eye. The maximum power setting used was −10dB and power output was continuously displayed on the screen.

Patients were in a semirecumbant position with a 15° left lateral tilt. Coupling gel was applied and the transducer was placed on the closed eyelid. Care was taken not to apply excessive pressure in order to avoid artifacts. Horizontal scans through the eye and orbit were performed. Flow toward the transducer was selected as red and away from the transducer as blue. This ensured that antegrade arterial blood flow appeared as red and venous flow appeared as blue. The colour saturation in the image indicated the average frequency (first moment average) from a spectral analysis performed at each sample site. The velocity was then automatically calculated from the frequency by the onboard software by solving the Doppler equation for velocity. 'Low' or 'medium' flow settings, sensitive to low and to intermediate Doppler frequency shifts, respecitvely, were used. Colour thresholds were adjusted to minimize artifact from involuntary lid and eye movements.

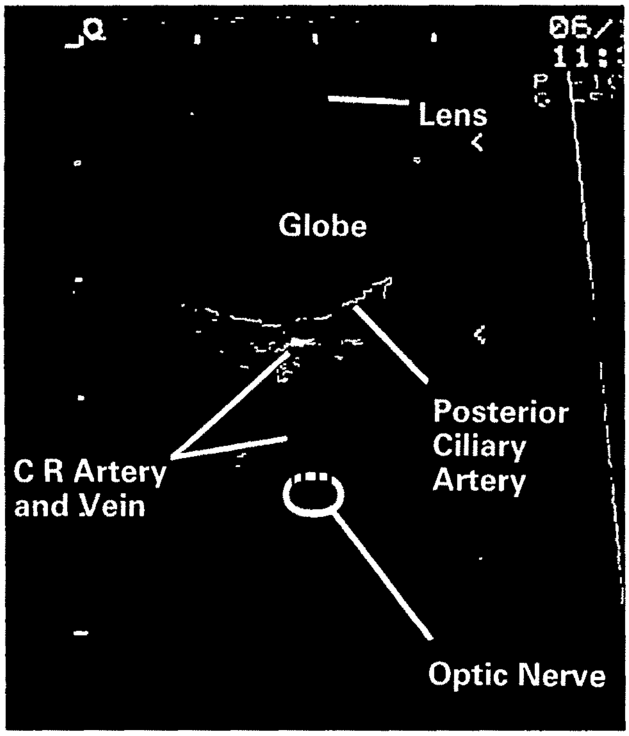

**Fig. 1.** Colour-flow sonograph showing the close approximation of the central retinal (CR) artery (red) and vein (blue). The posterior ciliary artery is shown coursing along the posterior surface of the globe of the eye. The optic nerve is represented by the ultrasound shadow in which the central retinal vessels run.

The globe was imaged in a plane that included the lens and the anterior 2 mm of the optic nerve, within which the central retinal artery and vein were clearly visible in all cases (Fig. 1). The central retinal artery was identified and traced to its point of entry into the optic nerve approximately 13 mm from the disc. An angle correction indicator was used to ensure an angle of insonation of the central retinal artery of <20° during spectral analysis. The software package of the Quantum 2000 system provided an angle-corrected mean-velocity measurement as well as a mean pulsatility index (PI) and Pourcelot resistance index (RI). Spectral analysis of the Doppler waveform was performed during a period of maternal apnoea, and the average velocities and Doppler indices from three waveforms were calculated at each determination. All waveforms and calculated indices were recorded on videotape and thermal paper.

After the baseline Doppler assessment was completed, a magnesium sulphate loading dose (6 g in 100 ml 5% dextrose-

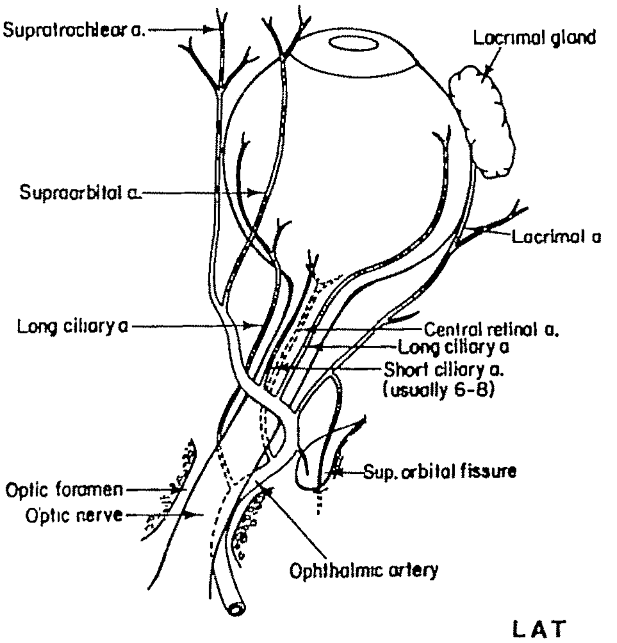

**Fig. 2.** The arterial blood supply of the orbit is shown. The relation of the central retinal artery to the long ciliary artery (also known as the posterior ciliary artery) is illustrated. LAT = lateral side of the orbit. (Reprinted with the kind permission of Dr S. J. Erickson and *Radiology*: from Erickson S. J., Hendrix L. E., Massaro B. M., Harris G. J., Lewandowski M. F., Foley W. D. & Lawson T. L. (1989) Color Doppler flow imaging of the normal and abnormal orbit. *Radiology* **173**, 511–516.

**Table 1.** Demographic data for eight women in the study

| | |
|---|---|
| Age (years) | 32 (5) |
| No. of pregnancies | 3 (1) |
| Gestational age (weeks) | 37 (4) |
| Proteinuria (Dipstix) | 3 (1) |
| Baseline systolic blood pressure (mmHg) | 151 (15) |
| Baseline diastolic blood pressure (mmHg) | 90 (9) |

Results are mean (SD) values

water) was infused for over 20 min. The Doppler studies were then repeated.

The mean velocity, mean PI and the RI from three waveforms were averaged at each measurement and recorded. Since both the left and right central retinal arteries were insonated, the average value was calculated and used for analysis purposes. No differences have been noted between measurements from right and left eyes in previous studies (Lieb *et al.* 1991).

Data were analysed using a two-tailed, paired Student's *t*–test and a $P$ value of $< 0.05$ was considered to be statistically significant.

Figure 1 shows the colour flow Doppler image of the retinal blood vessels, with the retinal artery and vein and the posterior ciliary vessels clearly seen. Fig. 2 shows a schematic diagram of the vessels in the orbit.

## Results

Eight consecutive patients with pre-eclampsia who were to receive magnesium sulphate as anti-seizure prophylaxis were studied (Table 1). Blood pressure and heart rate did not change significantly following the magnesium sulphate infusion.

Baseline and post-magnesium sulphate Doppler data from the patients are presented in Table 2. Data from the individual patients are presented in Figs. 3 and 4 which show baseline and post-infusion RI and PI values from both the central retinal and posterior ciliary arteries. There was a significant reduction in the central retinal artery PI ($P$ = 0·05; difference between the means = 0·48, 95% CI 0·001 to 0·96). The central retinal artery RI was also significantly lower after magnesium sulphate infusion ($P$ = 0·008; difference between the means = 0·09, 95% CI 0·03 to 0·15). There was a non-significant change in the mean central retinal artery blood velocity after magnesium sulphate infusion.

**Table 2.** Blood pressure and Doppler data before and after an infusion of magnesium sulphate in eight women with mild pre-eclampsis.

| | *n* | Baseline | After $MgSO_4$ | *P* |
|---|---|---|---|---|
| Blood pressure (mm Hg) | | | | |
| Systolic | 8 | 151 (15) | 151 (13) | NS |
| Diastolic | 8 | 90 (9) | 89 (6) | NS |
| Central retinal artery | | | | |
| Pulsatility index | 8 | 1 42 (0·67) | 0·93 (0·18) | 0·05 |
| Resistance index | 8 | 0·62 (0·07) | 0·53 (0·10) | 0·008 |
| Mean velocity (cm/s) | 8 | 17 (20) | 9 (5) | NS |
| Posterior ciliary artery | | | | |
| Pulsatility index | 8 | 0·97 (0·14) | 0·78 (0·18) | 0·01 |
| Resistance index | 8 | 0·58 (0·07) | 0·48 (0·09) | 0·02 |
| Mean velocity (m/s) | 8 | 20 (19) | 17 (7) | NS |

Results are mean (SD) values.

There was also a significant reduction in the posterior ciliary artery PI ($P$ = 0·01; difference between the means = 0·19, 95% CI 0·06 to 0·33). The posterior ciliary artery RI was significantly lower after magnesium sulphate infusion ($P$ = 0·02; difference between the means = 0·09, 95% CI 0·02 to 0·16). There was a non-significant change in the mean blood velocity after the magnesium sulphate infusion.

## Discussion

The retinal blood vessel changes seen in severe pre-eclampsia usually take the form of hypertensive retinopathy without organic evidence of arteriosclerosis. The first signs appear on the nasal side of the disk as focal and then generalized arteriolar spasm, initially transient, but later permanently affecting all of the arterioles (Hollwich 1979). Severe arteriolar spasm is the most common fundal finding in pre-eclampsia and may be evident in up to 70% of cases (Wagener 1933). Blindness in severe pre-eclampsia has been reported to originate from generalized spasm of the retinal arterioles (Ghandi *et al.* 1978), thrombosis of the central retinal artery (Carpenter *et al.* 1953), choroidal and retinal detachment (Kenny *et al.* 1972), and from acute ischaemic optic neuropathy due to impairment of the blood supply to the optic nerve head (Beck *et al:* 1980).

None of the patients in this study experienced abnormal visual symptoms, but this would not be expected to occur in mild disease. Focal vascular spasm may, however, be present without causing critical ischaemia. This phenomenon may explain the wide variation in the recorded flow-velocities. Some vessels were insonated distal to an area of focal vasospasm resulting in high velocities, while in other cases insonation proximal to a focal constriction resulted in low velocities. The mean flow-velocity curves for the central retinal artery and posterior ciliary artery have not yet been determined longitudinally during normal pregnancy. Lieb *et al.* (1991) studied 18 men and 12 non-pregnant women with a mean age of 45 (SD 16). Their subjects had lower flow-velocities (central retinal artery maximal systolic flow-velocity: mean 10·3, SD 2·1 cm/s; posterior ciliary artery maximal systolic flow-velocity: mean 12·4, SD 4·8 cm/s) than those seen in the women with pre-eclampsia in the present study. The hormonal contribution of pregnancy to retinal vessel relaxation, compounded with the focal vasospasm seen in pre-

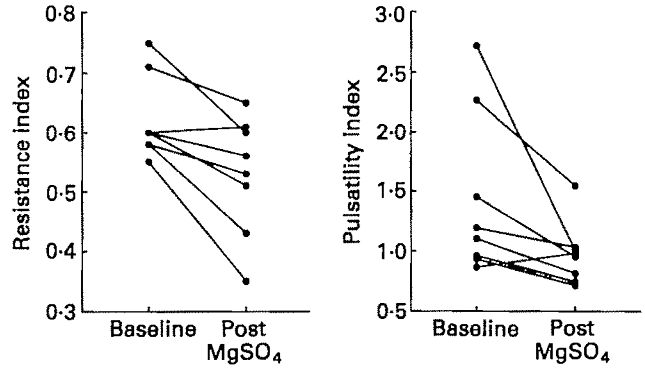

**Fig. 3.** Central retinal artery resistance and pulsatility index values before baseline and post magnesium and after an infusion of magnesium sulphate ($MgSO_4$) in eight pregnant women with mild pre-eclampsia.

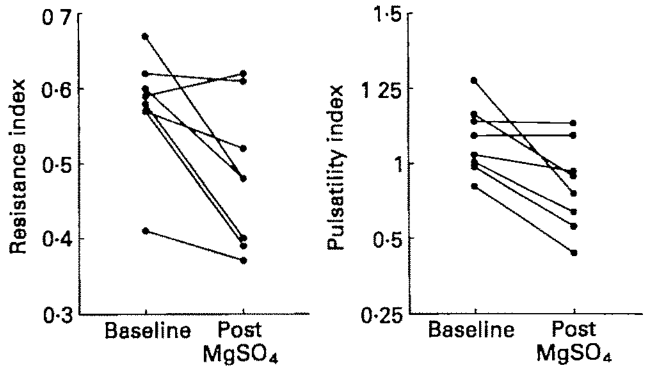

**Fig. 4.** Posterior ciliary artery resistance and pulsatility index values before and after an infusion of magnesium sulphate ($MgSO_4$) in eight women with mild re-eclampsia.

eclampsia, make meaningful analysis of flow-velocity data difficult at this time, and longitudinal data from normal pregnant women will be required. In addition, inaccuracies in quantitative measurements may result from errors in the interpretation of the Doppler-shifted frequency spectrum and from the measurement of the Doppler angle. Estimates of uncertainty associated with individual measurements of the maximum systolic velocity have been reported to be in the region of 18% using laser velocimetry, similar to most studies reporting Doppler flow data (Feke *et al.* 1989). In the present study reproducibility of data was good. This was confirmed by a good correlation of the indices obtained from analysis of three different waveforms obtained at three separate imaging times from each eye (less than 10% difference between the measurements).

The changes in PI and RI values allow assessment of the effect of the magnesium sulphate on the baseline values. A reduction in these indices, in both the central retinal and posterior ciliary arteries following the infusion of the drug, strongly suggests a lowering of the resistance in the vascular bed distal to the region of insonation. This may indicate an alleviation of vasospasm and retinal ischaemia, and offers an explanation for the improvement in visual disturbances often noted after initiation of magnesium sulphate treatment for pre-eclampsia.

Changes in intraocular pressure were not measured in this study and could potentially have contributed to the observed decreases in Doppler ratios. There is no published data on the effect of magnesium sulphate on intraocular pressure. Magnesium sulphate-induced vasodilatation has been shown to be related to calcium flux (Nadler *et al* 1987) and there is evidence to suggest that calcium channel blockers reduce intraocular pressure (Payne *et al* 1990) and improve retinal perfusion (Nihard 1982). Thus, magnesium sulphate may improve the retinal circulation by reducing intraocular pressure and relieving vasospasm.

Morphologically and physiologically, the retinal vessels are similar to those in the brain (Bill 1975). The endothelial cells of the capillaries are attached to each other by tight junctions. Blood flow through the retina is autoregulated, and the sympathetic nervous system has little effect on retinal perfusion (Bill 1975) Both the retinal and cerebral vascular beds are supplied by the internal carotid artery and both exhibit autoregulation within the normal mean arterial pressure limits. Preliminary data (Belfort *et al* 1992) from this institution have indicated that magnesium sulphate reduces the Doppler ratios in the vascular bed distal to the first portion of the middle cerebral artery in patients with pre-eclampsia. Magnesium sulphate is known to vasodilate constricted cerebral vessels (Altura & Altura, 1984) and, given the similarity of the retinal and the intracerebral vessels, the results of the present study indicate a similar response in the retina. Doppler waveform analysis may thus allow the non-invasive assessment of cerebral blood flow in vasospastic conditions by examintion of the retina. This is not a new concept in pre-eclampsia, but meaningful data have been difficult to accumulate due to the restrictions of the available technology. The advent of colour flow Doppler ultrasound may change this. Orbital vessels are readily accessible to Doppler investigation, and this technology may provide a valuable screening test for cerebral (and other small vessel) vasospasm. In addition colour flow Doppler may be useful in the assessment of the vascular and haemodynamic effects of fluid therapy and pharmacologic agents in a variety of pathologic conditions in pregnancy. Before the full potential of this technique can be realized, however, normative curves are needed to allow a better understanding of the changes occurring during normal pregnancy. In addition, placebo controlled studies will help in the assessment of both the reproducibility of the technique, and the effect of the agent being studied. It must be stressed that this report is a preliminary communication and that before clinical use further studies are required.

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OBSTETRICS

# Midpregnancy plasma zinc in normal and growth retarded fetuses—a preliminary study

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## ABSTRACT

**Objective** To determine plasma zinc concentrations in normally and abnormally growing fetuses.

**Design** Prospective observational study.

**Setting** Fetal Medicine Unit, Queen Charlotte's Maternity Hospital.

**Subjects** 53 pregnant women attending for fetal blood sampling at between 18 and 40 weeks gestation. 27 fetuses were normal (central group), 11 fetuses were growth retarded and 15 were malformed.

**Main outcome measures** Plasma zinc concentrations in maternal and fetal blood at time of fetal blood sampling.

**Results** In normally growing fetuses, between 18 and 40 weeks gestation, there was no fall in maternal plasma zinc concentration; the fetal level fell by 36%. In 10 fetuses with symmetrical growth retardation, plasma zinc concentration tended to be low, but was not significantly different from that in the normal control fetuses.

**Conclusion** The results suggest that (i) placental transfer of zinc is an uphill secretory process and that it is a rate-limiting step in the accumulation of zinc by the fetus and (ii) in fetuses with symmetrical intrauterine growth retardation, a low plasma zinc is probably a parallel phenomenon and not necessarily an aetiological factor.

Zinc is an essential element which is universally required by plants and animals for many physiological processes including nucleic acid and protein synthesis (Hurley 1977; Dreosti *et al.* 1985; Wu & Wu 1987). It is necessary for growth, and zinc deficiency is associated with short stature and dwarfism (Golden & Golden 1979). Animals fed zinc-deficient diets during pregnancy have shown an increased rate of pregnancy complications such as fetal loss, neonatal death and abnormal deliveries and a high incidence of fetal malformation and growth retardation (Hurley 1977; Dreosti *et al.* 1985; Golub *et al.* 1984).

Sandstead (1985) has shown that estimated average zinc intakes from Western diets are similar to average dietary requirements, indicating that intake may only be marginally adequate, or actually inadequate, in a significant proportion of these populations. Furthermore, in pregnancy, zinc requirement is increased. Low maternal mid-gestation plasma or term leucocyte zinc concentrations have been reported in women giving birth to infants with congenital malformations or intrauterine growth retardation (Buamah *et al.* 1984; Simmer & Thompson 1985a; Apgar 1985), although many other studies have failed to find such relations (Apgar 1985; Campbell-Brown *et al.* 1985; Ghosh *et al.* 1985; Jepson & Clemmensen 1987: Bro *et al.* 1988).

Maternal plasma or leucocyte zinc concentrations may not be good measures of the availability of zinc for fetal development because this presumably depends on the concentration of the species of zinc, not necessarily total plasma zinc (Bloxam *et al.* 1984; Bax & Bloxam, unpublished) transported across the placenta, and on the activity of the transfer process itself, as well as on fetal factors such as circulating zinc binding protein levels. It is, perhaps, not surprising that investigations of possible relations between maternal zinc and fetal growth abnormality have been inconclusive.

A more useful approach may be to measure fetal zinc directly. Meadows *et al.* (1983) have found peripheral blood leucocyte zinc to be low in growth retarded infants at birth, and Soltan & Jenkins (1982) found low plasma zinc in cord blood of a group of malformed infants. On the other hand neither Arumanaygam *et al* (1986), nor Bro *et al.* (1988) found a relation between cord plasma zinc concentration and birthweight although a positive correlation between cord tissue zinc and birthweight was observed. Zinc concentrations at term may not reflect those earlier in pregnancy at important periods of fetal development. The advent of fetal blood sampling has made it possible to measure mid-gestation fetal plasma zinc concentration, and this paper reports a preliminary study to determine values of zinc in normally and abnormally growing fetuses *in utero*.

## Subjects and methods

Plasma zinc was measured in 53 pregnant women and their fetuses, who were attending for fetal blood sampling between

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**Table 1.** Characteristics of 11 pregnancies with intrauterine growth retardation (IUGR)

| Type of IUGR | Gestational age at sampling (weeks) | Plasma zinc concentration (µmol/l) |  | Fetal outcome |  |
|---|---|---|---|---|---|
|  |  | Fetal | Maternal | Gestation (weeks) | Birthweight (g) |
| Symm | 31 | 19·1 | 15·1 | 31 (SB) |  |
| Symm | 36 | 13·4 | 11·2 | 37 | 1590 |
| Symm | 31 | 13·7 | 12·5 | 31 | 1668 |
| Symm | 34 | 13·8 | 10·4 | 34 | 1340 |
| Symm | 33 | 11·2 | 9·2 | 34 | 1380 |
| Symm | 31 | 16·2 | 15·9 | 32 (NND)* | — |
| Symm | 21 | 27·2 | 11·4 | Triploidy |  |
| Symm | 23 | 27·6 | — | 26 (NND)* | — |
| Symm | 23 | 21·9 | — | 28 (SB) |  |
| Asymm | 26 | 27·9 | 9·1 | 27 (SB) |  |
| Asymm | 23 | 22·3 | — |  |  |

*Born by caesarean section.

Abbreviations; Symm = symmetrical, asymm = asymmetrical, SB = stillbirth, NND = neonatal death.

18 and 40 weeks gestation. The indications for fetal blood sampling were intrauterine growth retardation (12), fetal structural malformations (21), maternal age (4), maternal toxoplasma infection (5) oligohydramnios (2), polyhydramnios (1) positive Down's syndrome screen test (3) and other miscellaneous indications (6). Pregnancies associated with non-immune hydrops (2) and Rh–isoimmunization (25) were excluded. According to the ultrasound examination and fetal karyotyping there were 27 normal fetuses (control group), 11 fetuses with intrauterine growth retardation (IUGR) (9 symmetrical and 2 asymmetrical growth retardation), and 15 malformed fetuses (6 with obstructive uropathy and 9 with structural malformations). Fetal biparetal diameter, abdominal circumference and femur length were measured by ultrasound at the time the blood samples were taken. Diagnosis of fetal growth retardation was based on fetal biometry less than the 10th centile for a given gestational age, whereas asymmetrical fetal growth retardation was considered to be present if the ratio of fetal head to abdominal circumference was >95th centile. Tables 1 and 2 give details of the IUGR and the structurally malformed fetuses, respectively.

The procedures were performed under ultrasound guidance using a 20 gauge needle, as described elsewhere (Nicolini *et al.* 1988), usually between 0900 and 1400 hours.

For assay of zinc about 1 ml of fetal blood was collected in an acid-washed plastic tube containing zinc free lithium heparin (10–15U/ml). At the same time, 2–3 ml of maternal venous blood were collected without the use of a tourniquet, with a disposable plastic syringe. Each specimen was centrifuged (1500 *g* for 10 min) and the plasma removed and stored in an acid washed plastic tube at –20°C. Haemolysed samples were excluded (7 maternal and 3 fetal samples, one from the normal, one from the obstructive uropathy and one from the structurally malformed fetuses).

Plasma zinc concentrations in the fetal and maternal plasma samples were measured by atomic absorption spectrophotometry with electrothermal atomization (AA-1475 spectrophotometer with GTA95 graphite furnace, Varian, Walton-on-Thames, UK) by the method of Foote & Delves (1982). In some cases measurement of albumin ($n$ = 20), alpha-fetoprotein ($n$ = 18) (Leek *et al.* 1975) and alkaline phosphatase ($n$ = 20) (Technicon RA system method no. SM4-0132J85) were also performed.

Plasma zinc values and the other biochemical measurements were normally distributed. A reference range (mean and 95% data interval) of fetal plasma zinc at 18–38 weeks was constructed from the control group. The least squares method was used to calculate the correlation between fetal and maternal plasma zinc concentrations and fetal zinc with fetal growth indices i.e., gestational age as determined by ultrasound, the estimated fetal weight, fetal biparietal diameter, head circumference, abdominal circumference, and femur length. Multiple

**Table 2.** Cases of structural malformation

| Anomaly | Gestation weeks | Plasma zinc concentration |  |
|---|---|---|---|
|  |  | Fetal | Maternal |
| Holoprosencephaly | 19 | 22·5 | 15·8 |
| Holoprosencephaly, Encephalocele, Multiple anomalies | 21 | 26·2 | 8·8 |
| Hydrocephalus | 20 | 26·9 | 8·2 |
| Hydrocephalus | 23 | 30·2 | 9·6 |
| Hydrocephalus, Short limbs | 21 | 27·5 | 5·9 |
| Hyperflexed hands, Small ventricles | 20 | 25·6 | 9·8 |
| Short upper limbs | 20 | 30·3 | — |
| Dilated stomach, Club foot | 20 | 19·3 | — |

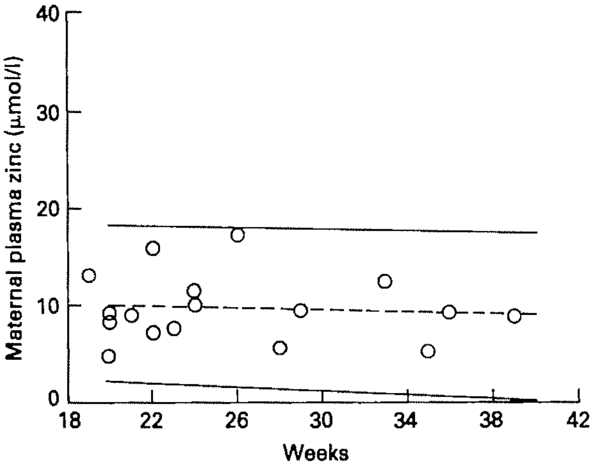

**Fig. 1.** Reference range (mean and 95% data interval) for maternal plasma zinc concentration derived from 17 normal pregnancies between 18 and 38 weeks gestation

regression analysis was used to examine the relation between plasma zinc concentration and biochemical and clinical variables. A $P$ value of $<0{\cdot}05$ was considered significant.

## Results

### *Maternal zinc*

Fig. 1 shows the range of maternal plasma zinc concentrations between 20 weeks (9·3 ± 3·7 μmol/l) and 36 weeks (8·1 ± 2·2 μmol/l) of pregnancy. Only 17 maternal blood samples were available for analysis (seven samples were haemolysed and three were not available). There was no evidence of a fall during this time. There also was no significant relation between maternal plasma zinc concentration and plasma alkaline phosphatase activities, nor with fetal plasma zinc, ultrasound measurements of fetal dimensions or estimated fetal weight.

### *Fetal zinc*

Fig. 2 shows the range of fetal plasma zinc concentrations between 18 and 38 weeks gestation in 26 normal pregnancies. There was a significant negative relation between fetal plasma zinc and gestational age ($r = 0{\cdot}6$, $P = 0{\cdot}001$). The estimated mean zinc concentration fell by 36% from 26·5 mol/l (95% CI 23·8 to 29·2) at 20 weeks to 17·1 μmol/l (95% CI 13·3 to 20·9) at 36 weeks.

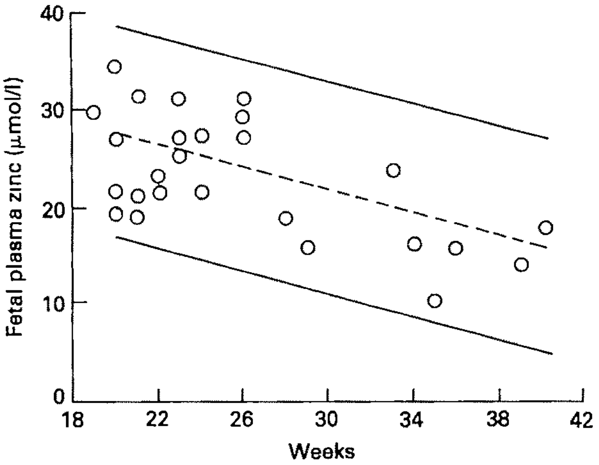

**Fig. 2.** Reference range (mean and 95% data intervals) for fetal plasma zinc concentration derived from 26 normal pregnancies between 18 and 38 weeks gestation ($y = 38{\cdot}3 – 0{\cdot}6$, $r = –0{\cdot}6$, $P<0{\cdot}001$).

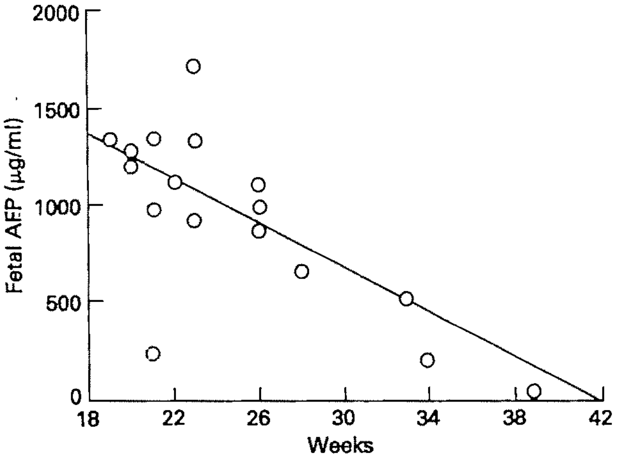

**Fig. 3.** Fetal plasma alpha-fetoprotein (AFP) concentrations between 18 and 40 weeks gestation ($y = 2431{\cdot}6–60{\cdot}1$, $r = 0{\cdot}73$, $P<0\ 001$)

Fetal plasma alpha-fetoprotein concentrations decreased significantly with gestational age (Fig. 3) and fetal plasma albumin increased (Fig. 4). Thus, fetal plasma zinc concentration showed a positive correlation with fetal alpha-fetoprotein ($P = 0{\cdot}03$) (Fig. 5), and a negative correlation with fetal plasma albumin ($P = 0{\cdot}006$) (Fig. 6) respectively, which were dependent on gestational age. Similarly there was a strong negative relation between plasma zinc and estimated fetal weight, also dependent upon gestational age ($P = 0{\cdot}0005$).

There was no relation between fetal plasma zinc concentration and ultrasound measurements of fetal dimensions except a gestational age-dependent inverse correlation with femur length ($P = 0\ 04$).

Fig. 7 shows the fetal plasma zinc concentrations in the abnormal fetuses with IUGR ($n = 11$), structural anomaly ($n = 8$) and fetal uropathy ($n = 5$) compared with the reference

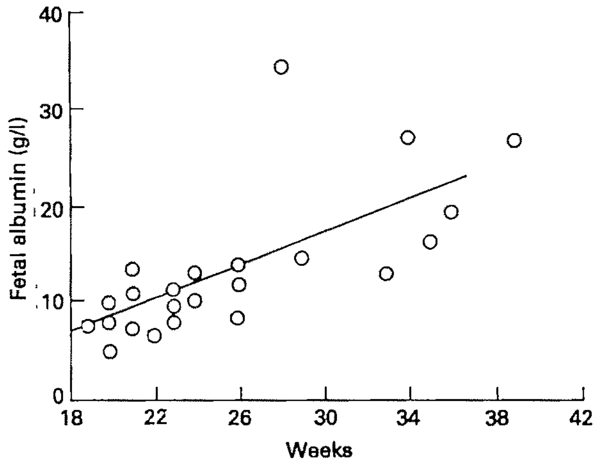

**Fig. 4.** Fetal plasma albumin concentrations between 18 and 40 weeks gestation ($y = 9{\cdot}4 + 0{\cdot}5$, $r = 0{\cdot}7$, $P<0{\cdot}0001$).

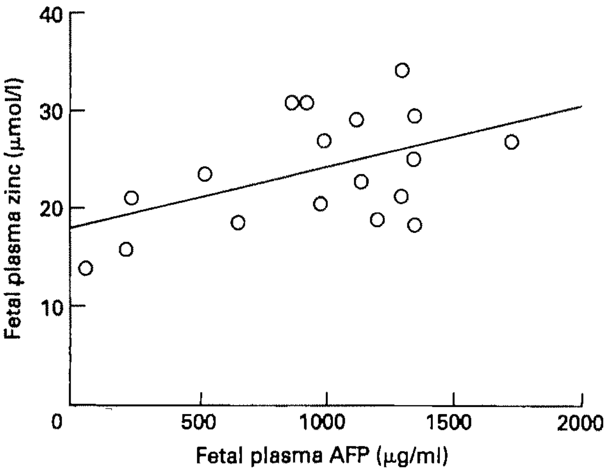

**Fig. 5.** Correlation between alpha-fetoprotein (AFP) and zinc concentrations in fetal plasma in 18 fetuses between 18 and 40 weeks gestation ($y = 18\cdot2 + 6\cdot3$, $r = 0\cdot5$, $P = 0\cdot03$).

mean and 95% data range derived from 26 normal pregnancies. The fetal plasma zinc values, and the ratios of fetal/maternal zinc concentrations were lower in the fetuses with symmetric growth retardation than in the control fetuses, but the differences were not significant. Fetuses with structural anomalies and fetuses with obstructive uropathy had no discernable pattern of plasma zinc distribution.

## Discussion

Normal fetal plasma zinc concentrations are, on average, significantly higher than maternal plasma levels between 18 and 38 weeks gestation; three-fold higher at 20 weeks and two-fold higher near term. The latter figure is in agreement with values found by others in cord blood plasma (Meadows *et al.* 1983; Bro *et al.* 1988). The fetal plasma concentration of the main circulating zinc binding protein, albumin, is lower than maternal plasma levels, and alpha-fetoprotein levels are at least an order of magnitude lower still, indicating that total zinc binding capacity is lower in the fetal than in the maternal circulation. Thus, placental transfer of zinc appears to be an active process during this period of pregnancy, especially at the earlier stages. This is consistent with the findings of Page *et al* (1988), who studied the perfused human term placental cotyledon, and Simmer *et al.* (1985) using the near-term perfused guinea pig placenta.

Maternal plasma zinc concentration is known to decline slowly during pregnancy (Hambidge *et al.* 1983; Apgar 1985; Campbell-Brown *et al* 1985; Ghosh *et al.* 1985). The substantial fall of fetal plasma zinc was not due to a change in albumin concentration, which in fact rose significantly during this time, might suggest that the fetal need for zinc (including that required to fill the expanding blood volume) outstripped the rate of placental transfer during this period of rapid fetal growth. This is consistent with the negative relation found between fetal plasma zinc concentration and estimated fetal weight. Thus, placental transfer appears to be a rate-limiting step in the accumulation of zinc by the fetus.

The lack of correlation between maternal and fetal plasma zinc concentration is in agreement with the observation of Meadows *et al.* (1983), at term, with a much larger number of subjects. It suggests that there is little or no rapid feto-maternal exchange of zinc. This finding, together with the other results mentioned above, indicate that placental zinc transfer is a relatively slow, secretory type of process (i.e., relatively irreversible with little exchange).

The positive relation of fetal plasma zinc and fetal alpha-fetoprotein is not surprising since the concentrations of both fell with time during gestation. Alpha-fetoprotein is unlikely to influence total plasma zinc concentration directly because its concentrations are so much lower than those of plasma albumin. Nevertheless, alpha-fetoprotein binds zinc more strongly than albumin, and has about twice as much high-affinity zinc binding capacity (Wu *et al.* 1979). Alpha-fetoprotein is produced, as the main fetal protein, very early in gestation by the yolk sac, then by the fetal liver, to reach a maximum concentration of about 3 mg/ml by the end of the first trimester before it starts to decline (Editorial 1979). These considerations together suggest the possibility that alpha-fetoprotein may

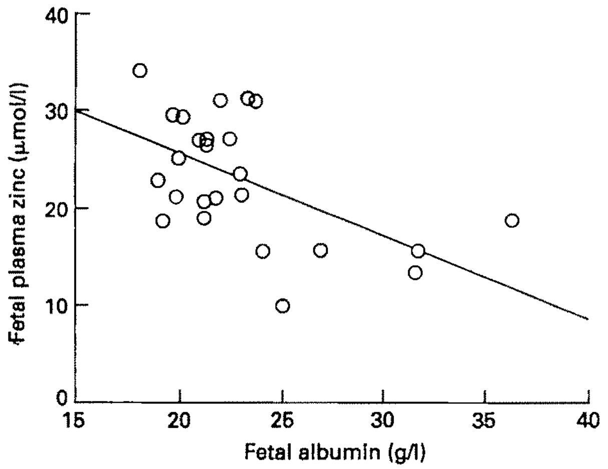

**Fig. 6.** Correlation between albumin and zinc fetal plasma concentrations in 25 fetuses between 18 and 40 weeks gestation ($y = 40\cdot8 - 0\cdot8$, $r = -0\cdot5$, $P = 0\cdot006$).

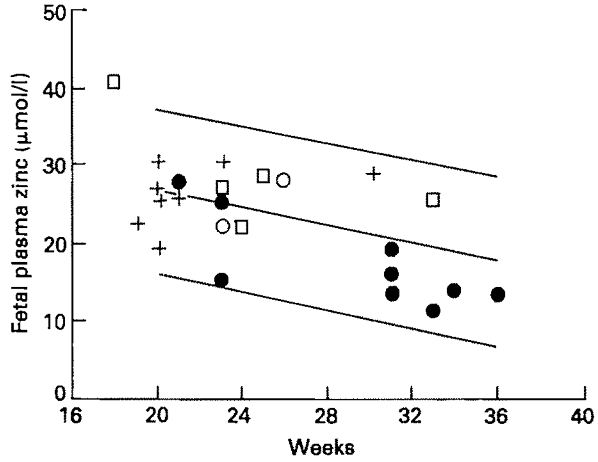

**Fig. 7.** Fetal plasma zinc concentrations in 24 abnormal pregnancies between 18 and 40 weeks gestation. Structural malformations (+), obstructive uropathy (□), symmetrical (●), and assymetrical (○) intrauterine growth retardation. The lines indicate the reference range (mean and 95% data intervals) derived from 26 normal pregnancies.

have a particular role in the acquisition of zinc by the fetus, especially early in pregnancy during hyperplastic phases of fetal development (Villar & Belizan 1982).

*Abnormal fetuses*

As placental release may be a limiting factor in the fetal accumulation of zinc, in theory, a sufficiently low maternal zinc availability for placental transfer or impaired placental transfer itself might reduce fetal zinc availability to an extent that interferes with fetal development. In this study, although there was a tendency to low fetal plasma zinc concentration in the fetuses with symmetrical IUGR, the level was not statistically different from the control group. The low plasma zinc in the growth retarded fetuses may therefore be a parallel phenomenon rather than a causative factor. Unfortunately, we have not studied enough fetuses with asymmetrical IUGR, which generally develops near term, to draw any conclusions. The present preliminary investigation provides no evidence to suggest a relation between abnormal fetal zinc disposition and fetal malformation. A larger number of fetuses with various forms of growth abnormalities will need to be investigated to clarify whether low fetal zinc is a cause, rather than merely a marker, of abnormal fetal growth.

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OBSTETRICS

# Placental bed biopsies in placental abruption

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**ABSTRACT**

**Objective** To investigate structural changes in the uteroplacental blood vessels in association with placental abruption.
**Design** Prospective descriptive study.
**Subjects** 18 women with clinical evidence of severe placental abruption delivered by caesarean section.
**Interventions** Placental bed biopsies were obtained at caesarean section and studied histologically.
**Results** Six specimens did not include trophoblast in the myometrium and were therefore not representative of the placental bed. Of the 12 representative specimens, seven demonstrated absence of physiological transformation of the utero-placental arteries (four of these were from hypertensive patients). Four biopsies showed abnormal vascular structures deep in the myometrium. One of these abnormal vessels included a fresh plug and extensive surrounding intramyometrial haemorrhage.
**Conclusions** Vascular malformations in association with placental abruption may be the result of trophoblastic invasion and could be the site of vessel rupture. Further descriptive and comparative studies are needed.

Placental abruption is an unpredictable, dramatic event with a 40–60% fetal mortality and considerable maternal morbidity. While the cause is unknown, the premature separation of the placenta and the intramyometrial haemorrhage probably result from the rupture of a utero-placental artery with extravasation of blood under arterial pressure between myometrial bundles. Blood tracking to the decidual surface causes placental separation and fetal hypoxia while haemorrhage towards the serosal surface produces the typical ecchymosis of the Couvelaire uterus (Couvelaire 1911). Whereas approximately 25% of women with placental abruption have hypertension (Brink *et al.* 1987; Abdella *et al.* 1984), most of them do not.

The possibility of a primary defect in the utero-placental vessels needs to be considered. The microscopic features of the placental bed in placental abruption have been described among larger series of placental bed biopsies (Dixon *et al.* 1958; Hustin *et al.* 1983), but there are no published reports dealing specifically with this topic. The purpose of this study was to record the findings in placental bed biopsies in a series of women with clinical placental abruption.

## Subjects and methods

### *Design*

Placental bed biopsies were obtained at the time of caesarean section from 18 women with clinical evidence of placental abruption confirmed by the presence of retroplacental clot at operation. The technique was that described by Robertson *et al.* (1986). The site of placental attachment was identified by the surgeon as soon as the fetus was born and marked by the assistant keeping a finger on the serosal surface opposite this area. After delivery of the placenta, this site was inspected for bleeding vessels, and a biopsy approximately 1 cm in diameter and 0·5 cm deep, including bleeding vessels where possible, was taken with a scalpel. A single haemostatic suture was inserted. No problems were encountered with this technique, except that it was more difficult to perform when the placenta was anteriorly situated. The specimen was formalin fixed and paraffin embedded. Sections were stained with haematoxylin and eosin, Victoria blue for elastic fibres, Martius scarlet blue for fibrin, Masson's trichrome, van Gieson, periodic acid Schiff/alcian blue and combinations thereof. The presence of extra-villous trophoblast within the myometrium was required to confirm that the biopsy was from the placental site. Vessels within the decidua were labelled superficial. Those at the junction of the decidua and myometrium were called intermediate and those completely surrounded by myometrium were labelled deep.

The study was approved by the ethics and review committee of the University of Cape Town and patient consent was obtained.

## Results

Of the 18 biopsies, six showed no trophoblast and were therefore regarded as not representative of the placental bed and excluded from further study. The main clinical and histological features of the remaining 12 women are summarized in Table 1.

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**Table 1.** Clinical and histological features in 12 women with placental abruption delivered by caesarean section

| | Subject number | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Age (years) | 35 | 19 | 33 | 24 | 34 | 22 | 25 | 19 | 25 | 17 | 19 | 23 |
| Gravidity | 6 | 1 | 3 | 2 | 3 | 1 | 2 | 1 | 5 | 1 | 1 | 1 |
| Gestation (weeks) | 30 | 31 | 37 | 32 | 36 | 34 | 40 | 34 | 32 | 35 | 32 | 34 |
| PIH | Yes | No | Yes | No | No | Yes | Yes | No | No | No | No | Yes |
| Outcome | A | A | A | SB | A | A | SB | A | A | SB | A | SB |
| Trophoblast | ++ | + | + | + | ++ | + | + | ++ | ++ | ++ | ++ | ++ |
| Endomet glands | – | + | – | + | – | + | + | +/– | + | – | – | – |
| Myohaemorrhage | – | – | +/– | +/– | +/– | +/– | +/– | + | + | ++ | ++ | ++ |
| UP artery int | 2 | 1 | 1 | – | – | 1 | – | 1 | 1 | 1 | 1 | 1 |
| Phys change int | – | + | – | – | – | – | – | – | + | – | + | + |
| UP artery deep | – | – | 2 | 1 | 2 | 1 | 1 | – | 1 | 1 | 1 | – |
| Phys change deep | – | – | – | – | + | – | – | – | – | – | – | – |
| Atherosis | – | – | + | – | – | – | – | – | – | – | – | – |
| Sub int fibrosis | – | – | + | – | + | + | – | – | ++ | + | – | – |
| Vasc malformation | – | 1 | – | – | – | – | – | – | 1 | 1 | – | 1 |

Symbols: –, absent; +/–, minimal; +, moderate, ++, marked; numerals 1 or 2 refer to the number of vessels present.
Abbreviations: UP artery = Uterine placental artery; intermediate (int) or deep. Phys change = Physiological change Sub int = Sub intimal fibrosis within arteries. PIH = Pregnancy-induced hypertension. Myo haemorrhage = Intramyometrial haemorrhage Outcome A = livebirth; SB = still birth.

Microscopic examination showed abundant extra villous trophoblast in seven of the 12 biopsies. This was largely composed of multinucleate cells but mononuclear cytotrophoblastic cells could also be found. The other five biopsies contained fewer trophoblastic giant cells and in one of these there were only isolated cells. In four of these latter five biopsies and in two of the first seven, there were endometrial glands on the surface.

Haemorrhage was present in 10 of the 12 biopsies. In five there were only small focal collections of red blood cells lying between muscle fibres. In three biopsies haemorrhage was very heavy. In one of these the haemorrhage was predominantly superficial with only moderate haemorrhage in the myometrium. In a second biopsy there was abundant haemorrhage on both the surface and between muscle bundles (Fig. 1) and in the third it was largely confined to the myometrium. In the remaining two specimens the haemorrhage was assessed as moderate.

At least one uteroplacental artery was seen in the myometrium in each biopsy. In five biopsies these showed transformation with replacement of the media by trophoblast and fibrin (the so-called physiological changes). One of these transformed vessels had a layer of sub-intimal fibrin around 50% of its circumference and another showed a marked narrowing rather than dilatation of the lumen due to an accumulation of fibrin within the media. The uteroplacental arteries in the remaining seven biopsies showed no physiologic changes although trophoblast was present near the periphery of the vessels and in one instance a single trophoblastic cell was present within the wall. Four of these seven women were hypertensive.

In three intermediate and two deep arteries there was an eccentric intimal fibrosis associated with an accumulation of acid mucopolysaccharide. Two of these arteries (one intermediate and the other deep) showed physiological changes; the other three did not. Four deep uteroplacental arteries showed medial hypertrophy. Two of these four biopsies (nos. 6 and 7) were from women who were hypertensive. In another hypertensive women (no. 3) one deep vessel showed acute atherosis with lipophages and fibrin within the media.

In five of the biopsies the veins showed trophoblast around the periphery, close to the media but not associated with any fibrin or other changes to the media (Fig. 2).

In each of four biopsies there was an unusual vascular structure in the myometrium (Fig. 3). Although differing in size and detail they all showed similar features. There was a markedly dilated vessel which for the most part resembled a vein with a thin wall which contained no elastic lamina, trophoblast or fibrin (Fig. 4). In areas the wall was widened by sub-intimal fibrosis. In three of these vessels, fibrin and trophoblast were seen deep to the subintimal thickening. In the fourth vessel there were occasional trophoblastic cells but no fibrin. The dilated portion in all four contained a recent thrombus. These vessels differed from these usually seen in the placental bed and were interpreted as possible vascular malformations. Near

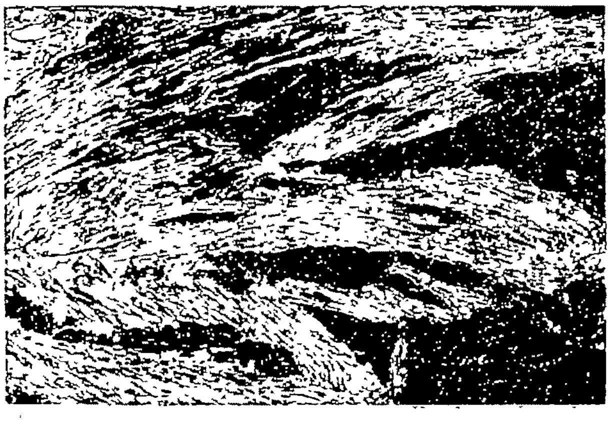

**Fig. 1.** Haemorrhage tracking between myometrial fibres. H&E×75).

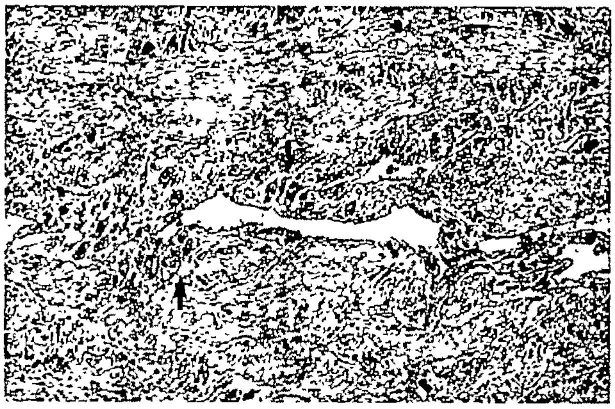

**Fig. 2.** Intramyometrial vein showing trophoblast (arrows) in the wall but no fibrin and no transformation. (H&E × 75).

two of these malformations there was marked intramyometrial haemorrhage and in one this appeared to arise from the abnormal vessel (Fig. 5).

## Discussion

This is essentially a descriptive study of the placental bed in women with placental abruption undertaken in an attempt to identify the origin of the intramyometrial bleeding and to examine the uteroplacental vessels with a view to identifying a possible causative anomaly. One of the problems with placental bed biopsies for such a study is sampling. Of the 18 biopsies, only 12 contained trophoblast and six of these showed some endometrial glands on the surface which might indicate that the biopsy came from near the periphery of the placental bed. Whereas abnormal vessels, if present, could as easily be near the edge as the centre, their presence or absence in the biopsy may be due to chance sampling. Moderate to severe intramyometrial haemorrhage, in keeping with the clinical diagnosis of placental abruption, was present in five biopsies.

The vascular abnormalities included an absence of normal physiological changes in the myometrial portion of the uteroplacental arteries in seven biopsies, intimal or sub-intimal thickenings in five and abnormal or malformed vessels in four.

The absence of physiological transformation of the myometrial portion of uteroplacental arteries is associated with gestational hypertension (Khong *et al.* 1986). Five of the women in this study were hypertensive and four of them showed an absence of arterial transformation. The other three biopsies which showed a lack of transformation were from normotensive pregnancies.

Intimal or sub-intimal thickenings were found in the uteroplacental arteries in five biopsies as well as in the four vessels regarded as malformed. In three instances the thickenings occurred in arteries not showing physiological transformation. These intimal thickenings are morphologically similar to the cushions described by Brosens *et al.* (1967) who suggested that they may be the result of previous thrombosis. However, their presence in deeper non-transformed arteries in the myometrium suggests that they could also be jet lesions caused by increased or turbulent blood flow. That they are seen frequently in pregnancy indicates that they are not specifically related to placenta abruption. Brosens *et al.* (1967) also describe these thickenings in veins. Apart from their presence in the four lesions regarded as possible vascular malformations, which may be of venous origin, sub-intimal thickening was not observed in any of the other intramyometrial veins in this study.

In four biopsies there were very dilated vessels lying within the myometrium. Brosens *et al.* (1967) described superficial veins in the placental bed as being widely dilated with walls showing the presence of fibrin and a loss of normal architecture. The four abnormal vessels in our study might represent a partial extension of this superficial transformation of veins into the intramyometrial portion of the vessel.

The precise nature of these vessels was not clear, but they resembled veins with a thin wall without much elastica and no internal elastic lamina. In these areas there was a normal-looking media with no evidence of transformation, no trophoblast or intramural fibrin. In places, however, deep in the wall beneath focal intimal thickening, there was fibrin and trophoblast. Sub-intimal fibrosis and recent non-occlusive thrombi were present in all four biopsies. While these changes were not always in opposition, it is tempting to conclude that the intimal

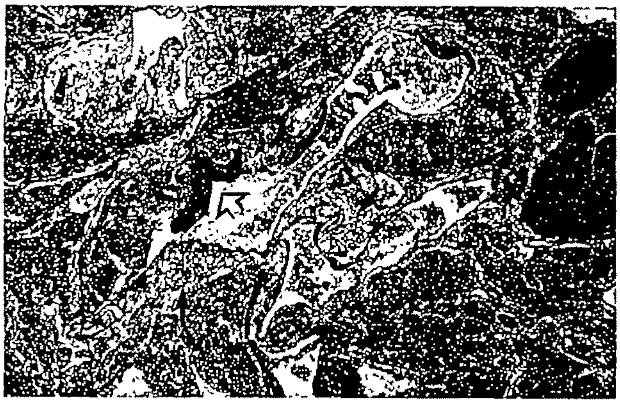

**Fig. 3.** Vascular malformation. A large complex vessel with thin wall in places and intimal fibrosis (closed arrow) elsewhere. Numerous smaller channels are present at the periphery. Recent thrombus (open arrow) is present. (Trichrome × 20).

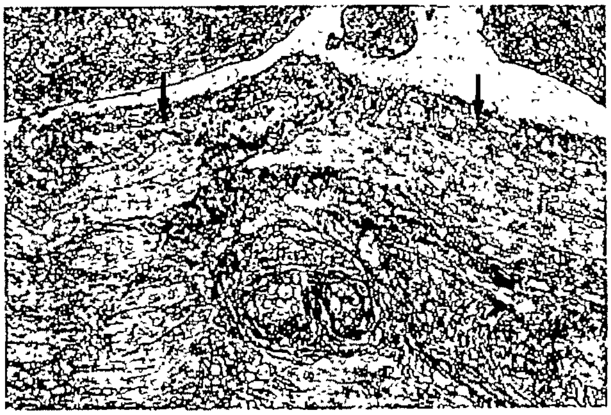

**Fig. 4.** The wall of the vascular malformation (arrows) contains no elastic tissue. A basal artery in the centre acts as positive control. (Victoria blue × 150).

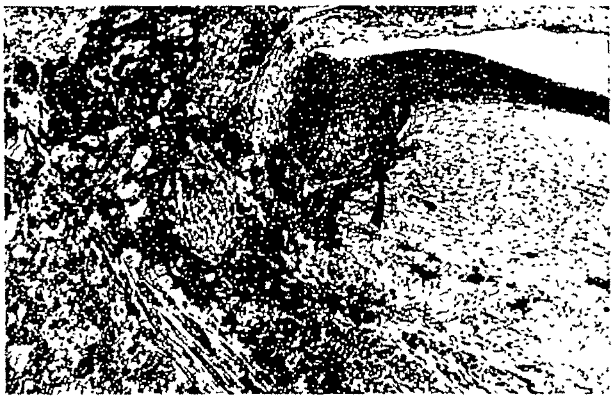

Fig. 5. Haemorrhage apparently coming from a vascular malformation. Sub-intimal fibrosis is present on the right. A fibrin platelet thrombus (arrow) is present at the site of haemorrhage. (H&E × 75)

thickening is the result of organization of previous mural thrombosis. However, the intimal thickenings are morphologically similar to those seen in deeper radial arteries of the placental bed where they might be better interpreted as jet lesions which are due to increased or turbulent flow; this raises the possibility that these vascular abnormalities could be arteriovenous anastomoses.

Heavy intramyometrial haemorrhage was present near two of these malformed vessels and in one instance the haemorrhage appeared to arise from the vessel. Burchell & Mengert have suggested that bleeding from veins might be responsible for the premature separation of the placenta but it would seem unlikely that venous pressure would be sufficient to cause the intramyometrial extravasation seen in placental abruption. Robertson (1987) reports the occasional finding of arteriovenous malformations in hysterectomy specimens from patients with antepartum haemorrhage. His illustration does not show quite the same appearance as the lesions seen in the present study but it is possible that the structures seen in our study represent arteriovenous communications and the sub-intimal fibrosis could represent attempts at 'arterialization' of veins subject to arterial pressures. Haemorrhage from such a vessel may well be under sufficient pressure to track between muscle fibres.

Arteriovenous malformations within the uterus are not common. They may be developmental and have also been described as a consequence of carcinoma, gestational trophoblastic disease and trauma following surgery (Fleming *et al.* 1989). It is tempting to speculate that if the malignant trophoblast of choriocarcinoma can produce arteriovenous communication; this may occur occasionally with the physiological invasion of blood vessels in normal pregnancy. Robertson (1987) suggested that the invading trophoblast sometimes may produce distorted or abnormal architecture.

The significance of vascular malformations merits investigation. There is a need for comparable biopsies from the placental bed from pregnancies uncomplicated by placental abruption. If further studies can show that these vessels are the source of the original bleeding in placental abruption, additional factors will need to be identified to explain the higher frequency of placental abruption in women of lower socioeconomic status.

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GYNAECOLOGY

# The modified Pereyra procedure: a clinical and urodynamic review

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**ABSTRACT**

**Objective** To review the clinical and urodynamic outcome of treatment by the modified Pereyra procedure in 93 women with genuine stress incontinence.
**Design** Retrospective review.
**Setting** Harbor/UCLA Medical Center and Los Angeles County Women's Hospital, Los Angeles, California, USA.
**Main outcome measures** Clinical and urodynamic assessment one year after modified Pereyra procedure.
**Results** Overall 82% of patients were subjectively cured while only 63% were objectively cured. Women with failed surgery had significantly lower pre-operative maximum urethral closure pressures. The procedure had a low operative and post-operative morbidity with no significant disturbance of voiding function noted at one year follow-up.
**Conclusions** Our results with the modified Pereyra procedure for stress incontinence showed a significantly lower success rate than has been reported from many previous studies.

Since their introduction by Pereyra (1959), transvaginal needle suspension procedures for stress incontinence have become very popular operations. Due to lack of clear objective criteria to define a surgical success or failure, cure rates for these procedures range from 40-97% (Mundy 1983; Stamey 1973; Raz 1981). Most of these studies used subjective criteria in the form of the patients' own opinion to measure the results of treatment. The use of urodynamic recording techniques, such as simultaneous urethrocystometry and urethral pressure profilometry, have not only provided objective criteria for diagnosis but they have also allowed the determination of different indices of importance in the assessment of stress incontinence. To date, very few large studies with good follow-up of clinical and urodynamic indices exist.

The following study was undertaken to review clinical and urodynamic outcome of the modified Pereyra procedure in 93 women with genuine stress incontinence.

## Subjects and methods

Ninety-three women with a primary complaint of urinary incontinence, with or without symptoms of genital prolapse, were studied. Forty-four women were seen and operated on at Harbor/UCLA Medical Center and 49 at Los Angeles County Women's Hospital. At each center the women studied were

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**Table 1.** Comparison of pre-operative and postoperative urodynamic variables

| Variables | Pre-operative | Post-operative | *P* value |
|---|---|---|---|
| MUCP (cm $H_2O$) | 43 (21) | 39 (19) | NS |
| UFL (cm) | 3·1 (1·4) | 3·3 (1·3) | NS |
| PTR in proximal Urethra (%) | 71 (13) | 99 (10) | $P<0·05$ |

Values are mean (SD), MUCP = maximum urethral closure pressure; UFL = urethral functional length; PTR = pressure transmission ratio; NS = not significant.

consecutive cases with genuine stress incontinence in which follow up for at least one year was available. There were no other selection criteria. The average age of the women was 48 (range 31–81) years and their average parity was 5 (range 1–7); 44 were premenopausal and 49 were postmenopausal.

All of the women underwent a systemic diagnostic assessment which included a history and physical examination, urine culture, Q-tip test (Karram & Bhatia 1988), cysto-urethroscopy, standing provocative water urethrocystometry, and static and dynamic urethral pressure profilometry. Urethral pressure measurements were performed with microtip catheters which were mechanically withdrawn through the urethra with the sensor oriented in the lateral position at nine o'clock. Pressure transmission ratios were calculated by taking the maximum cough spike in the proximal urethra and dividing the urethral spike by the bladder spike and multiplying by 100. For a woman to be given the diagnosis of genuine stress incontinence it was mandatory that there be direct observation of urine loss from the urethra during coughing with urodynamic evidence of pressure equalization between the bladder and urethra in the absence of any rise in true detrusor pressure.

All of the women underwent the modified Pereyra procedure which included all the modifications of the original techniques (Pereyra *et al.* 1982). Special emphasis was placed on the inclusion of the pubo-urethral ligament and endopelvic fascia at the level of the proximal urethra and bladder neck, the use of prolene sutures, and endoscopic control of the elevation of the urethrovesical junction while tying sutures to avoid undue urethral compression. Forty women also had a vaginal hysterectomy and 69 women had either an anterior or a posterior colporrhaphy, or both. None of the women had had previous anti-incontinence surgery. All procedures were performed under the supervision of one of the authors.

**Table 2.** Comparison of pre-operative demographic and urodynamic variables in successful and or failed surgery

| Variables | Cured ($n$=59) | Failed ($n$=34) | *P* value |
|---|---|---|---|
| Age (years) | 47 (10·5) | 51 (12) | NS |
| Parity | 5 (3·1) | 5 (3·3) | NS |
| Menopausal status | | | |
| Premenopausal | 28 (57%) | 16 (36%) | NS |
| Postmenopausal | 27 (55%) | 22 (49%) | NS |
| UFL (cm) | 3·0 (1·5) | 3·0 (1·2) | NS |
| MUCP (cm $H_2O$) | 44 (24) | 34 (13) | $P<0·05$ |
| PTR in proximal urethral (%) | 71 (13) | 67 (14) | NS |

Values are mean (SD) or *n* % of group as appropriate; UFL = urethral functional length; MUCP = maximum urethral closure pressure, PTR = pressure transmission ratio; NS = not significant.

All of the women had a complete clinical and urodynamic assessment repeated 12 months after their Pereyra procedure. A subjective cure was defined as denial of any urinary leakage, whether stress or urge related. An objective cure was defined as absence of urinary leakage in the standing position at the time of urodynamic testing, whether due to genuine stress incontinence, detrusor instability, or a combination of both.

All terminology conforms to that proposed by the International Continence Society (Abrams *et al.* 1988). $\chi^2$- analysis, Student's $t$-test, and Mann-Whitney $U$-test were used for statistical analysis of the results.

## Results

All 93 women had urodynamically confirmed genuine stress incontinence with a stable bladder. One year after the procedure 76 women (82%) denied any urinary leakage and were classified as subjective cures, whereas 59 were continent at the time of urodynamic testing giving an objective cure rate of 63%.

When pre-operative and postoperative urodynamic data were compared, there was no significant change in maximum urethral closure pressures or in functional length. There was, however, a statistically significant increase in abdominal pressure transmission to the proximal urethra (Table 1). Bladder neck mobility, which was assessed using the Q-tip test, revealed the average maximum straining angle to be 62° (SD 21) pre-operatively and this decreased to 41° (SD 23) postoperatively ($P<0·05$). Six women (7%) developed detrusor instability postoperatively.

In an attempt to determine which women were at higher risk of failure of the procedure, pre-operative demographic and urodynamic variables of women whose operation failed were compared with those who were objectively cured. There were no significant differences in age, parity, menopausal status, urethral functional length or pressure transmission ratio between these two groups. However, women with failed surgery had significantly lower pre-operative maximum urethral closure pressures (Table 2).

There were no significant differences in the subjective or objective cure rates for women who had only Pereyra procedures compared with those who also had other procedures.

Complications which occurred are listed in Table 3. Retention was defined as the need for bladder drainage for $>7$ days following surgery. At one year follow-up, all the women were voiding spontaneously with low postmicturition residual volumes ($<50$ ml). Infection was defined as febrile morbidity requiring intravenous antibiotics for $>48$ h.

**Table 3.** Complications of Pereyra procedure in 93 patients

| Complications | No of patients |
|---|---|
| Retention of urine | 14 (15%) |
| Infection | 11 (12%) |
| Blood loss requiring transfusion | 6 (6%) |
| Inadvertent cystotomy | 2 (2%) |

## Discussion

The results of this series show that although the modified Pereyra procedure is easy to perform with a low morbidity rate, its success in curing stress incontinence is not as high as that reported in some previous studies. This study also confirms that investigators cannot rely on subjective criteria in the form of the women's own opinion to determine success or failure since the cure rate was much lower when objective urodynamic criteria were used.

Other recent studies on needle suspension procedures using objective criteria have also noted cure rates substantially lower than some earlier reports. English & Fowler (1988) and Kirby & Whiteway (1989) reported objective cure rates of 58% and 75% respectively, 3–6 months after the Stamey procedure. Peattie & Stanton (1989) noted only a 40% success rate after a Stamey procedure in women over the age of 65 years. Two recent prospective randomized studies comparing anterior colporrhaphy, modified Pereyra procedure, and retropubic urethropexy in women with stress incontinence, with or without associated genital prolapse, also noted significantly lower cure rates with the vaginal procedures compared with abdominal bladder neck suspensions (Bergman *et al.* 1989a; Bergman *et al* 1989b).

Very few studies have examined other untoward effects of these procedures. Anti-incontinence surgery should only be performed when the incontinence is adversely affecting the woman's quality of life. Curing one problem only to create others such as severe urgency or urge incontinence, urinary retention or recurrent urinary tract infection which may be as troublesome as the initial stress incontinence, would not be satisfactory. When these factors have been assessed, success rates have been noted to be even lower (Mundy 1983).

Bladder instability must be conscientiously sought when anti-incontinence surgery is contemplated, as it has been shown to coexist in 5–30% of women with genuine stress incontinence (McGuire & Savastano 1985; Karram & Bhatia 1989). The postoperative course of bladder instability after anti-incontinence surgery is very unpredictable as it may persist, worsen, improve, or develop *de novo*. This has been studied more thoroughly after retropubic abdominal bladder neck suspension than after needle suspension procedures (Cardozo *et al.* 1979). In our series, instability developed *de novo* in six women (7%).

Why do the needle suspension procedures result in lower objective cure rates than abdominal retropubic suspensions since both types of procedure are aimed at elevating and stabilizing the bladder neck in a retropubic position? One explanation may be that the needle suspension procedures are more commonly performed in older, postmenopausal women with a greater degree of genital prolapse. Older women may have more pronounced atrophic changes in the urothelium which is unable to provide a urine-tight seal, despite adequate bladder neck elevation and enhanced abdominal pressure transmission. However, our study does not support this theory as there was no significant difference in cure rates in pre- and postmenopausal women. Another explanation could be that the needle suspension procedures are not as effective as abdominal retropubic suspensions in elevating and supporting the bladder neck. Our data support this theory since all women who had a recurrence of stress incontinence had a poorly supported bladder neck (maximum straining angle >30° on a Q-tip test). We also noted, and it has been reported previously (Crist *et al.* 1969), that there was a group of women who remained continent after surgery even though they had a recurrence of the anatomic defect of their bladder neck at least as severe as it was before the surgery. It is clear that the mechanism of cure in anti-incontinence surgery is still poorly understood.

The only pre-operative feature which was significantly different in the successful and failed surgery groups was the maximum urethral closure pressure. The concept of women with low resting urethral closure pressure being at higher risk of failure of conventional anti-incontinence surgery has been proposed before (McGuire 1981; Sand *et al.* 1987).

This retrospective study on the modified Pereyra procedure revealed an objective cure rate of only 62% at one year follow-up. All of the women who had persistence or recurrence of stress incontinence had a poorly supported bladder neck.

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GYNAECOLOGY

# A simplified method of laparoscopic presacral neurectomy for the treatment of central pelvic pain due to endometriosis

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## ABSTRACT

**Objective** To describe optimal procedures and preliminary results for videolaparoscopic presacral neurectomy as part of the surgical treatment of endometriosis associated with intractable dysmenorrhoea.

**Design** Observational study with follow up for at least one year.

**Setting** Subspecialty practice: Endometriosis Clinic and Centre for Special Pelvic Surgery.

**Subjects** Eighty five women (18–45 years) with endometriosis and intractable pain, referred because medical and surgical management had failed. Subjects without a central (midline) component to their discomfort were excluded.

**Interventions** Excision and vaporization of endometriotic pathology was followed by presacral neurectomy.

**Outcome measures** During surgery, severity of endometriosis was assessed using revised American Fertility Society scoring. Overall pelvic pain and dysmenorrhoea relief were determined by office visit, telephone interview and questionnaire at a minimum of one year postoperatively.

**Results** There were no operative complications and all women left hospital within 24 h of surgery. Overall pain relief was reported by 49 (94%) of 52 patients followed. The other three subjects noted no pain abatement. Dysmenorrhoea was reduced in 48 (92%) whereas four (8%) women claimed no relief.

**Conclusions** Laparoscopic presacral neurectomy is an option for treating dysmenorrhoea and pelvic pain in selected women, but is indicated only if medical management has failed. Videolaparoscopic presacral neurectomy using the $CO_2$ laser is safe in trained hands. Pain relief achieved is within the range reported for laparotomy.

Though surgical interruption of pelvic autonomic afferent nerves to combat serious dysmenorrhoea was independently described by Jaboulay (1899) and Ruggi (1899), a variety of more apt procedures, well reviewed by Fontaine & Herrmann (1932), subsequently evolved. Among them was ablation of the superior hypogastric plexus by Cotte (1925) to ameliorate pelvic pain. While controversy that has been evident from the beginning concerning case selection, variability in the anatomy (Elaut 1933; Davis 1936; Labate 1938) and results achieved remains unresolved (Black 1964; Tjaden *et al.* 1990, Vercellini *et al.* 1991), we deemed it appropriate to study the effects of presacral denervation in women with endometriosis and severe uterine pain, referred because medical and surgical management had proven inadequate. Accordingly, we have devised procedures using the $CO_2$ laser, hydrodissection and videolaparoscopy to treat endometriosis and a variety of other pelvic pathologies (Nezhat *et al.* 1991; Nezhat & Nezhat 1989, 1991). Our purpose here is twofold: firstly, to describe the laparoscopic methods employed in 85 women thus far and, secondly to summarize early results in the 52 patients treated since the project was initiated in September, 1989.

## Subjects and methods

The 85 subjects included in the study were between 18 and 45 years of age and had been referred with endometriosis and severe pelvic pain unresponsive to medical and surgical treatment. All had severe dysmenorrhoea and some also had adnexal or other discomfort. Those without prominent menstrual pain were excluded.

Preoperative and immediate postoperative routines were those for videolaparoscopic gynaecological surgery (Nezhat & Nezhat 1989, 1991). Prophylactic antibiotics and general endotracheal anaesthesia were used and the presacral neurectomies followed any surgical intervention necessary to treat pelvic disease. For research and record purposes, all procedures were video and audio taped. Fifty-two of the patients have been followed for a minimum of 12 months through office

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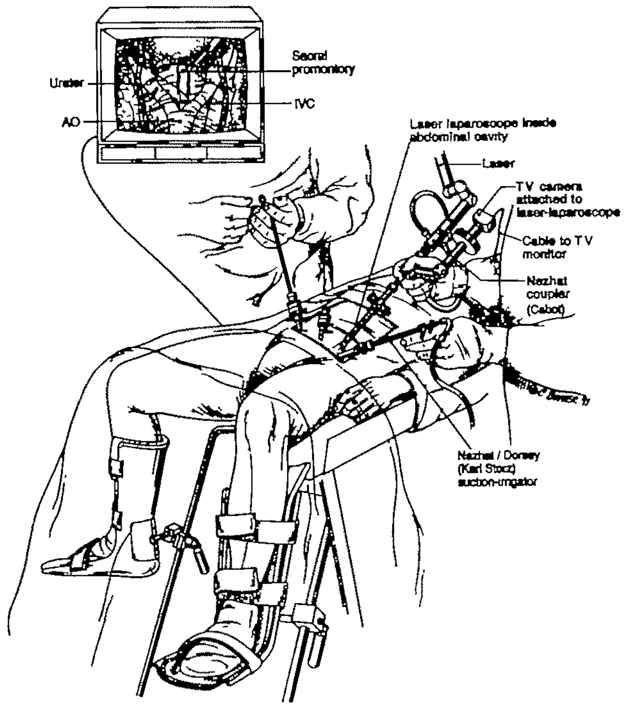
Sacral promontory
Ureter
IVC
AO
Laser laparoscope inside abdominal cavity
Laser
TV camera attached to laser-laparoscope
Cable to TV monitor
Nezhat coupler (Cabot)
Nezhat / Dorsey (Karl Storz) suction-irrigator

**Fig. 1.** Room set-up

visits, telephone interviews and a questionnaire. There were two pain relief assessments: one for 'overall' pain relief; the other specifically and *only* for dysmenorrhoea.

*Videolaparoscopic presacral neurectomy*

After establishing a pneumoperitoneum, an operating laser laparoscope (Karl Storz) was inserted through a 10 mm trocar (Ethicon, Somerville, NJ) placed through an umbilical incision. A 5·5 mm second puncture trocar (Ethicon) was placed in the midline approximately 4 cm above the symphysis pubis. Through this, a suction irrigator (American Surgical Instruments, Delray Beach, Florida) was introduced to remove smoke and char created by the laser and to serve as a backstop for the $CO_2$ laser beam. A third, and if necessary a fourth trocar were inserted 7·5 cm lateral to the suprapubic midline trocar to introduce grasping forceps, bipolar electrocoagulator or other necessary instruments (Fig. 1). The $CO_2$ laser, delivering its beam through the operating channel of the laparoscope (Coherent, Palo Alto, CA or Lasersonics, Milpitas, CA) via a direct lens was used at a power setting of 30–100 W in superpulse or ultrapulse mode for excision, ablation and hemostasis.

Steep Trendelenburg position was employed to keep the bowel away from the operating field. Following identification of the aortic bifurcation, the common iliac arteries and veins, the ureters and the sacral promontory, the peritoneum overlying the promontory was elevated with grasping forceps and a small opening made with the $CO_2$ laser (Fig. 2). Through this the suction irrigator was inserted and the peritoneum elevated by hydrodissection (Nezhat & Nezhat 1989). The peritoneum was incised horizontally and vertically and the opening extended cephalad to the aortic bifurcation. Bleeding from peritoneal vessels was controlled with the $CO_2$ laser or bipolar electrocoagulator. Within the triangular area known as the interiliac trigone, the following critical structures were identified: the left common iliac vein forming the floor of the left side of the pre-lumbar space defined; the inferior mesenteric, superior hemorrhoidal and mid sacral arteries. As noted by Elaut (1933), this trigone is defined caudally by the sacral promontory and laterally by the common iliac arteries meeting at the aortic bifurcation above. The midsacral artery lies in the midline and very near, or on the peritoneum. Centrally and to the left, multiple nerve fibres, sometimes in bundles, run from the aortic plexus above, caudally, through the interiliac trigone to form the superior hypogastric plexus. They continue inferiorly to comprise the inferior hypogastric plexus. These fibres, the so called presacral nerve, are buried in loose areolar tissue. They display no particular patterns and are variable from woman to woman (Fig. 3). Using blunt dissection and the laser, the nerve fibres were skeletonized and extraneous tissue removed. Nerve fibres, bundles and sheaths were cauterized and excised with the $CO_2$ laser (Fig. 4). It is important to remove all of the nerves between the two ureters that lie within the boundaries of the interiliac triangle, including any fibres entering the area from under the common iliac arteries (Fig. 5).

Finally, the retroperitoneal space was copiously irrigated and bleeding points controlled with the $CO_2$ laser or bipolar electrocoagulator. No sutures were used on the plexiform nerves or to approximate the edges of the peritoneum. Excised tissue was sent for histological examination to verify removal of nerve elements.

## Results

For the 85 patients, the duration of surgery was 45–185 min including the presacral neurectomies. Time for the latter ranged from 5 to 18 min. Blood loss was minimal. No intraoperative or immediate postoperative complications were noted. Most women were discharged on the day of surgery. Some remained overnight for convenience, but all left hospital within 24 h of surgery.

Fifty two patients have been followed for at least one year. Table 1 shows estimated pain relief achieved for 31, 13, 5 and 3 patients with minimal, mild, moderate and severe endometriosis, respectively (revised American Fertility Society 1985). Also given is the age distribution for each group, ranging from a mean of 27·4 years for minimal to 35·3 years for severe

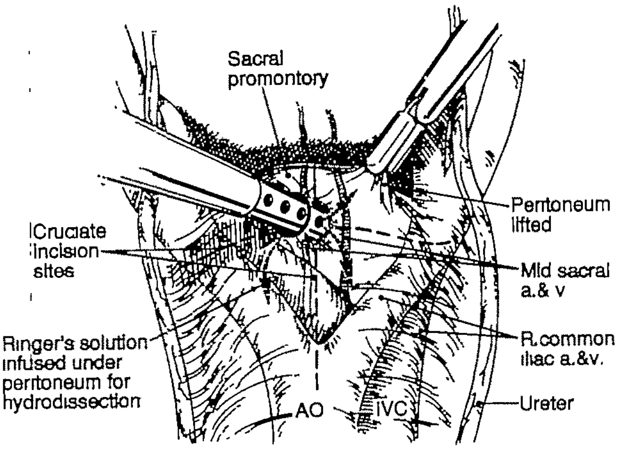

**Fig. 2.** Peritoneum being lifted and incision sites.

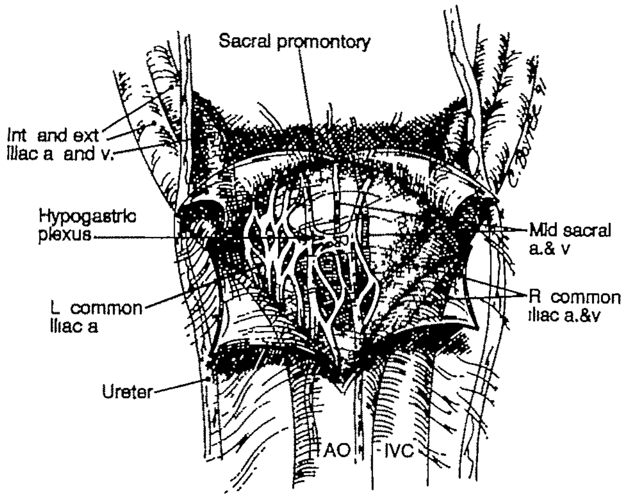

**Fig. 3.** Hypogastric plexus.

disease. Seven women had minor complications: constipation (3), urine urgency (1), vaginal dryness (1), 'painless' labour (2), one with very little pain and the other felt backache but no cramping pain.

Of the 31 patients with minimal endometriosis (Table 1) 16 (52%) reported 100% relief of dysmenorrhoea. Ten (32%) and 3 (10%) judged relief at 50–80% and less than 50%, respectively. Two women stated they experienced no relief at all.

Of 52 patients followed, 4 (8%) noted no relief of dysmenorrhoea, the other 48 (92%) reported some relief and 27 of these reported 100% relief of dysmenorrhoea. Of these 27 patients, 16 (67%), 6 (25%) and 3 (12%) had minimal, mild and moderate endometriosis, respectively.

Patient estimates of 'overall' relief of dysmenorrhoea and of any other pelvic pain were essentially similar to those for dysmenorrhoea. In contrast to the four women experiencing no relief of dysmenorrhoea, there were three who obtained no overall relief. Small sample constraints discourage emphasizing any other differences between overall pain relief and dysmenorrhoea relief but, taken together, one can speculate there may be a 50–50 chance for long-term, complete pain alleviation in selected patients with endometriosis undergoing a presacral neurectomy at the same time as thorough surgical treatment of coexisting endometrial and other pelvic pathology.

## Discussion

The most favourable results reported with presacral neurectomy to treat pelvic pain described only 2% failures in 1500 selected patients (Cotte 1949). In contrast, Black (1964) reviewed 2516 patients described between 1936 and 1963 in the world literature where primary and secondary dysmenorrhoea had been treated by presacral neurectomy. Good results were noted in 70%, 19% were improved and 11% were not improved. More recently, Lee *et al.* (1986) tabulated data from 11 studies of pelvic denervation (1939–1985) involving 576 patients, including 40 of their own. The combined figures reveal a 74% success rate (range 53–89%). Partial success occurred in 14% (range 6–13) and failures in 12% (range 6–12). Thus the pain relief achieved in the present study is well within the published range. It is relevant that Perez (1990) has also described a laparoscopic approach for presacral neurectomy, though he used an umbilical laparoscope to retract the bowel. Results in 25 patients with endometriosis with dysmenorrhoea, in which adnexal pain was minimal and medical treatment unsatisfactory, were assessed using a 0–10 pain scale. The mean preoperative score was 8·4 (7–10) compared with a post-surgical figure of 2·2 (0–8). Initially, all patients had incapacitating pain keeping them from school or work, and, with one exception, each resumed and maintained near normal activity over a follow-up period of 3–12 months. The only complication noted was one example of retroperitoneal haemorrhage requiring laparotomy.

Any attempt to compare presacral neurectomy by open laparotomy with laparoscopy is premature. Suitable data are sparse and there has been no consistent and clearly defined collection of information of the results obtained thus far by laparotomy.

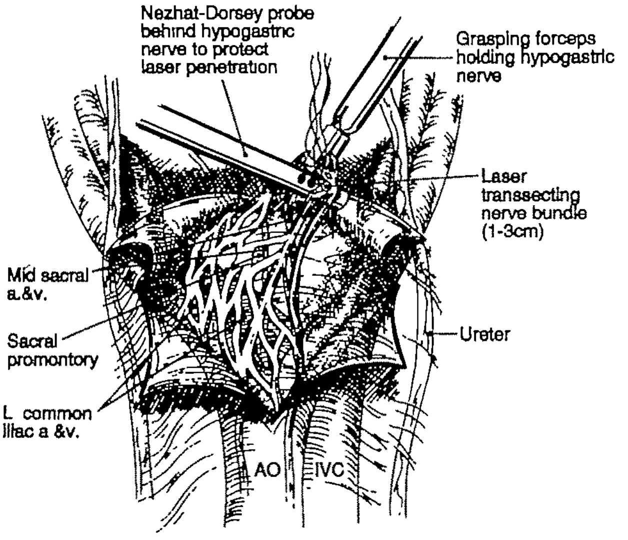
Nezhat-Dorsey probe behind hypogastric nerve to protect laser penetration
Grasping forceps holding hypogastric nerve
Laser transsecting nerve bundle (1-3cm)
Mid sacral a.&v.
Sacral promontory
L common iliac a &v.
Ureter
AO
IVC

**Fig. 4.** Transecting nerve bundle.

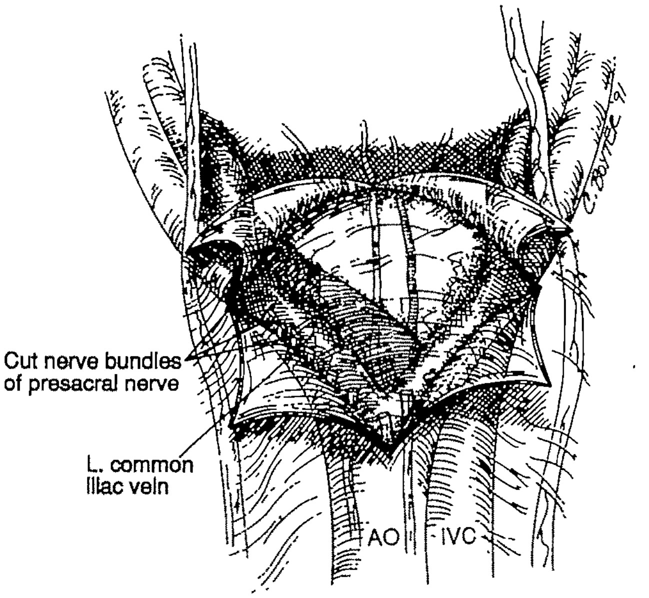

**Fig. 5.** Sacral promontory after neurectomy.

**Table 1.** Patient estimated relief of menstrual/overall pelvic pain at a minimum of one year after surgery

| Stage of endometriosis* | Patients n (%)† | Age (years) mean (range) | Estimated % relief | Dysmenorrhoea relief n (%) | Overall pelvic pain relief n (%) |
|---|---|---|---|---|---|
| Minimal | 31 (60) | 27·4 (18–38) | 100 | 16 (52) | 17 (55) |
| | | | 50–80 | 10 (32) | 7 (22) |
| | | | <50 | 3 (10) | 5 (16) |
| | | | 0 | 2 (6) | 2 (6) |
| Mild | 13 (25) | 33·6 (33–39) | 100 | 6 (46) | 6 (46) |
| | | | 50–80 | 6 (46) | 4 (31) |
| | | | <50 | 0 (—) | 2 (15) |
| | | | 0 | 1 (8) | 1 (8) |
| Moderate | 5 (10) | 30·5 (22–34) | 100 | 3 (60) | 2 (40) |
| | | | 50–80 | 2 (40) | 0 (—) |
| | | | <50 | 0 (—) | 3 (60) |
| | | | 0 | 0 (—) | 0 (—) |
| Severe | 3 (9) | 35·3 (31–45) | 100 | 2 (67) | 2 (67) |
| | | | 50–80 | 0 (—) | 0 (—) |
| | | | <50 | 0 (—) | 1 (33) |
| | | | 0 | 1 (33) | 0 (—) |

*Revised American Fertility Society staging (American Fertility Society 1985).
†Percentages may not total 100 due to rounding.

There has been confusion over the anatomical nomenclature. The Cotte operation was not presacral, but pre-lumbar. The presacral nerve is not, except perhaps rarely, a single nerve bundle. Rather, what the surgeon obliterates is the superior hypogastric plexus. The procedure is not only a sympathetic afferent neurectomy but includes severence of afferent fibres as well, particularly those concerned with vascular control, along with other nervous elements, the functions of which are not known.

Also, the Cotte procedure was first used to combat pelvic pain of obscure aetiology because the adage: 'physiologic function depends upon anatomic structure' led gynaecologists to believe that removal of the superior hypogastric plexus was not indicated for back pain or that associated with ovarian pathology, but might be effective for dysmenorrhoea, dyspareunia and vaginal discomfort. Thus from the beginning (and even currently) pelvic denervation surgery was empirical. Cotte, who did the first 'presacral neurectomy' in December 1924, understood this very well for he wrote: 'In the absence of precise and certain physiologic data concerning the nature and origin of the presacral nerve (superior hypogastric plexus of Hovelacque) it is difficult to explain the successful results obtained by presacral sympathectomy' (Cotte 1937). Unfortunately, the statement is applicable today even though a great deal of effort, much of it inter-disciplinary, has been expended to improve understanding.

For instance Elaut (1933), Davis (1934), Labate (1938) and Curtis *et al.* (1942), among others, reported results based on 50, 60, 75 and 30 cadaver dissections, respectively. The gross findings were variable and together emphasized the case-to-case differences to be expected. One study noted that fibres of the superior hypogastric plexus were not found on the right but were present in 75% and 50% to the left and in the midline, respectively, of the interiliac triangle. Another found the plexus to be on the left or central in one or two thirds of women. In 8–15%, the mesocolon was over the triangle, making neurectomy impossible or very difficult. A single nerve was observed in 8–13% of the early reports, reviewed by Fontaine & Herrmann (1932). Labate (1938), in an informative review of 95 dissections, noted a plexus in 84%, parallel nerve trunks in 8% and single nerves in 8%. Black (1936) described 27 presacral neurectomies and found 3 (11%) had single nerves and 23 (85%) plexiform arrangements. Davis (1933) in 20 operative cases, reported an accessory ureter lying in the midline. It is germane that Lichten & Bombard (1987), in a prospective, double blind study of the efficacy of laparoscopic uterine nerve ablation to alleviate dysmenorrhoea, noted that half the patients showed complete relief over a 12 month period. They speculated that failures were likely to be due to anatomical variations, including nociceptive afferents coursing centrally with the pelvic arteries. In fact, after reviewing the presacral neurectomy studies described by Black (1964) and the uterosacral nerve results reported by Doyle (1955) they stated that a failure rate of 30% could be expected as a result of anatomical variations between patients.

Uterine enervation remained an enigma. In his seminal review of uterine physiology, Reynolds (1965) noted 'There are no published data which show the course of the sensory nerves from the uterus to the central nervous system.' He did, however, note relief of uterine pain followed severance of the hypogastric nerves, making it probable that sympathetic afferents from the uterus were involved. It is important that Bonica (1990), contrary to prior teaching, has shown sacral afferent sensory fibres do not supply the lower uterus and cervix. Rather, segmental pain enervation of the uterine fundus, lower uterine segment and cervix involve T-10, T-11, T-12 and L-1. Uterine fibres travel centrad in order through the uterine, cervical and inferior hypogastric (pelvic) plexuses, then the middle and superior hypogastric and aortic plexuses to course upwards through the lower thoracic sympathetic chain. They reach the appropriate dorsal horn interneurons via communicating rami with the parent spinal nerve roots. These findings were derived from a study over 22 years of 240 deliveries in 35 women, utilizing a variety of segmental, regional and local anesthesia blocks to interrupt afferent transmission pathways. These data may have a bearing upon post-neurectomy complications involving the bowel and bladder whose central connections are through the lumbar and sacral roots.

A comprehensive review by Janig & McLachlan (1987) provides further understanding of pelvic innervation, in particular a quantitative classification of preganglionic neurons in splanchnic nerves. Of these, 15% were estimated to be vaso constrictive in function, 41% motor and 44% unclassifiable in that they were not involved in demonstrable local reflexes. Most of the latter were silent to electrical stimulation and were assumed to be involved in reproductive organ physiology, possibly through the release of bioactive substances.

Janig & McLachlan (1987) also suggested that there were local and regional autonomy and redundancy in the control of pelvic mechanisms. Data based on frequency distribution of neurons, functional activity of fibres with similar biophysical characteristics and biochemical coding, indicated that activity patterns, arising in the spinal cord or at higher levels, were transmitted via different routes from the cord to target areas. It appeared that both lumbar and sacral enervation were important in control of the bladder and colon. Functional disturbances occurred in animals if lumbar fibres were reduced or eliminated, but motor evacuative function was preserved when sacral elements remained intact. These findings are not inconsistent with what is known about bladder and colon complications following presacral neurectomy, but are insufficient to help surgeons achieve a zero complication rate.

Finally, it is important to keep in mind that presacral neurectomy does little to improve adnexal pain (Perez 1990; Tjaden *et al.* 1990) and, therefore, should be reserved for patients with central pain or intractable dysmenorrhoea. Given these complications, it is essential that patients are carefully assessed before surgical management. Only properly selected patients who have failed medical therapy should be considered.

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GYNAECOLOGY

# Laparoscopic treatment of infiltrative rectosigmoid colon and rectovaginal septum endometriosis by the technique of videolaparoscopy and the $CO_2$ laser

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**ABSTRACT**

**Objective** To present the technique and results of videolaparoscopy and the $CO_2$ laser as a treatment for deep, infiltrative endometriosis of the rectovaginal septum, uterosacral ligaments, pouch of Douglas and anterior wall of the rectosigmoid colon.
**Design** Observational study with 1–5 year follow up.
**Setting** Sub-specialty practice: Endometriosis clinic and centre for special pelvic surgery.
**Subjects** 185 women, ages 25–41 years. All had pelvic endometriosis and were referred because of the failure of previous medical and/or surgical treatment.
**Interventions** Vaporization and excision of endometriotic implants and nodules, ureterolysis, ureteric stents, laparoscopic anterior rectal wall resection and reanastomosis, presacral neurectomy, laparoscopic hysterectomy, salpingo-oophorectomy and appendicectomy using the $CO_2$ laser.
**Main outcome measures** 174 patients were followed for 1–5 years after surgery by office visit questionnaire or telephone interview. Eleven were lost to follow-up.
**Results** 175 patients were discharged within 24 h. Nine with bowel perforations and one with a partial bowel resection were discharged 2–4 days postoperatively. Two patients required ureteric stents, which were removed 6 weeks postoperatively without sequelae. 162 women reported moderate to complete pain relief (145 after one procedure, 13 after two and four after three). 12 reported persistent or worse pain following the surgery. Seven eventually underwent total hysterectomy, four had bowel resections and one had a salpingo-oophorectomy. Of 61 with infertility, 25 achieved pregnancy. Postoperative complications included shoulder pain, anterior abdominal wall ecchymosis, urine retention and dyschezia for one to two weeks.
**Conclusions** Our experience suggests that rectosigmoid colon and infiltrative rectovaginal septum endometriosis can be effectively treated via videolaparoscopy in the hands of experienced endoscopic gynaecologists.

Severe endometriosis commonly involves the uterosacral ligaments, rectovaginal septum and the rectosigmoid colon with partial or complete obliteration of the pouch of Douglas. This extensive degree of disease causes low pelvic pain, back pain, dysmenorrhoea, dyspareunia with diarrhoea, constipation, and dyschezia, but rarely rectal bleeding. Numerous investigators have explored the origin, pathology and treatment of this condition (Sampson 1940; Comille *et al.* 1990). Medical approaches are unsatisfactory. Correction and dissection by laparotomy are the usual surgical treatments, and have been reported to provide satisfactory pain relief and an acceptable pregnancy rate (Coronado *et al.* 1990). Endoscopic laser surgery has recently been used but its application has been limited in extensive disease because of lack of training in the technique and the perceived inability to palpate endometriotic nodules in order to facilitate safe removal.

Videolaparoscopy, using the $CO_2$ laser through the operating channel of the laparoscope as a 'long knife' (Nezhat *et al.* 1991a), has considerable advantages, particularly when combined with the laparoscopic magnification and control consequent on video monitor observation. It is an effective treatment for advanced endometriosis in the hands of experienced endoscopic gynaecologists. We report our experience in treating deep colorectal endometriosis with this technique.

## Subjects and methods

A total of 185 patients, ages 25 to 41, were managed between January 1985 and January 1990. These women had endometriosis of the lower colon, the rectum, uterosacral ligaments or the rectovaginal septum. All were referred for treatment because previous surgical or hormonal management had failed to relieve their discomfort. In 154 women, the presenting symptoms were chronic pelvic pain with dysmenorrhoea, dyspar-

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eunia, back pain, dyschezia, constipation or diarrhoea. Sixty one had infertility and pelvic pain. Thirty nine patients with histories of rectal bleeding were also investigated by sigmoidoscopy and 144 had a barium enema before laparoscopy. Eighteen women had previously undergone hysterectomy with or without salpingo-oophorectomy.

Each patient had the following outpatient bowel preparation: two days preoperatively, the patient consumed clear liquids. The evening before surgery, each drank a gallon of Go-Lytely (Braintree Laboratories, Braintree, MA) during 3–4 h (GoLytely contains polyethylene glycol, $Na_2So_4$, $NaHCO_3$, NaCl and KCl); at approximately 2300 hours, she took 1 g of metronidazole orally. Two grams of cefoxitin sodium were administered 30 min before the scheduled procedure. All the women were counselled regarding the possibility of a laparotomy, colostomy or bowel resection.

The procedures were performed at an outpatient service under endotracheal general anesthesia in the modified dorsolithotomy position as described in the previous article (Nezhat & Nezhat 1992). After the induction of the pneumoperitoneum and insertion of the operating laser laparoscope (Karl Storz, Culver City, California) two or three suprapubic punctures were made for the insertion of the ancillary instruments (Nezhat 1986, Nezhat *et al.* 1991g; Nezhat & Nezhat 1992). A miniature camera was attached to the laparoscope (Circon ACMI., Stamford, Connecticut). The $CO_2$ laser (Lasersonic, Milpitas, California or Coherent, Palo Alto, California) was connected to the laparoscope via the direct lens. The power of the $CO_2$ laser was between 40 and 100 W. The assistant stood between the patient's legs performing rectovaginal examination with one hand. The assistant's other hand held the uterus up with a curette, a dilator or the Humi rigid uterine elevator while both the assistant and surgeon observed the monitor. For rectovaginal septum and uterosacral ligament endometriosis, 5–8 ml of diluted vasopressin (10 units in 100–200 ml of lactated Ringer's solution) were injected into an uninvolved area with a 16 gauge laparoscopic needle. An opening was then made in the peritoneum with the $CO_2$ laser. A Nezhat (Cabot Medical) or a Nezhat-Dorsey (American Surgical Instruments, Inc., Delray Beach, Florida) probe was used to perform hydrodissection by means of pressurized lactated Ringer's solution forming a plane in the rectovaginal septum (Nezhat *et al.* 1989c).

While the assistant examined the rectum, the area of involvement was completely excised or vaporized until the loose areolar tissue of the rectovaginal space or normal muscularis layers of the rectum were reached. For patients whose rectum was pulled up and attached behind the cervix between the uterosacral ligaments, the uterus was first anteflexed sharply, then an incision was made at the right or left pararectal area and extended to the junction of the cervix and the rectum. For cases in which the involvement of the rectum was more extensive and the assistant's finger was not long enough, a sigmoidoscope, a sponge on forceps or a rectal probe was used. Two advantages to using the sigmoidoscope are: (i) it helps the surgeon identify the rectum and (ii) it aids in identifying or ruling out bowel perforation as this results in air bubbles passing from the air-inflated rectum into the pouch of Douglas which has been filled with irrigation fluid. While the assistant guided the surgeon by rectovaginal exam, the rectum was completely freed from the back of the cervix. At times, generalized oozing and bleeding occurred. This was controlled with an injection of 3–5 ml diluted vasopressin solution (1 ampule in 100 ml), laser or bipolar electrocoagulator. Occasional bleeding from the stalk vessels caused by dissection or vaporization of the fibrotic uterosacral ligaments and pararectal areas was controlled with bipolar electrocoagulator. Almost all patients had some bleeding but this was always controlled by the techniques described above.

Location and assessment of the ureters before proceeding with this procedure is of paramount importance, especially when they are infiltrated by endometriosis. Any alteration in the direction of the ureters should be identified in advance. Because ureters are lateral to the uterosacral ligaments, we try to stay between the ligaments as much as possible. Using hydrodissection and making a relaxing incision lateral to the uterosacral ligament allows the ureters to retract laterally. This affords increased protection of the ureters. Different degrees of ureterolysis were often necessary to free the ureters from the surrounding fibrotic, endometriotic tissue and from ovarian endometriomas. Endometriomas (in this group, up to 25 cm in diameter) were often densely attached to the bowel and ureter, and had to be freed. Hydrodissection (Nezhat *et al.* 1989c) along with the $CO_2$ laser and blunt dissection were used for ureterolysis, enterolysis and ovarian cystectomy. We rarely use sharp scissors, fibre lasers, unipolar electrode or hot scissors for these dissections.

Nodularity in the pouch of Douglas and infiltration of the endometriosis towards the vagina was dealt with by vaporization and dissection while the assistant checked the nodule by palpation until it completely disappeared (Nezhat *et al.* 1991b). There is a possibility of a perforation in the vagina, which can be left alone as long as the perforation is less than 1 cm. For cases in which the involvement was more severe, partial vaginectomy and repair were required. Endometriosis rarely penetrates the mucosa of the colon; but commonly involves the serosa, subserosa and muscularis. When significant portions of both muscularis layers have been excised or vaporized and the mucosa is reached, the bowel wall may be reinforced by one to three 4.0 polydioxanone sutures. This disease can be excised or vaporized very thoroughly by an experienced videolaparoscopist. The procedure is very demanding and maximum cooperation between the assistant and surgeon is necessary.

We search for possible rectal perforations with the sigmoidoscope (Nezhat *et al.* 1991b; Nezhat *et al.* 1992b), as described before, or by injecting indigo carmine or sterile milk into the rectum with a Foley catheter. Small perforations can be repaired laparoscopically with three to four interrupted 3–0 silk or 4–0 polydioxanone sutures (PDS) (Ethicon) (Nezhat *et al.* 1991b; Nezhat *et al.* 1992b). Consultation with a colorectal surgeon is always recommended. Most patients had involvement of other pelvic organs which were treated at the same time.

## Results

Excluding nine patients with bowel perforation and one with a partial bowel resection (Nezhat *et al.* 1991b) all were discharged within 24 h. The procedures (from initial laparoscopy to termination) lasted from 55 to 245 minutes. All patients were instructed to have nothing by mouth for 24 h postoperatively, except for sips of water, and if no complications were noted, the diet was gradually increased. Patients with bowel perforation or resection were allowed nothing by mouth until they had passed flatus and, otherwise, were instructed to avoid constipation by eating a high fibre diet. The patients were examined at one and six weeks after the operation.

Of 185 patients, 33 had rectovaginal septum involvement only, 22 had fibrotic and nodular uterosacral ligaments, 50 had partial and 80 had complete pouch of Douglas obliteration. During the procedure (Nezhat & Nezhat 1991b), 11 patients with severe nodularity of the rectovaginal septum had small, vaginal perforations. No sutures were applied. In nine patients, the rectosigmoid colon was entered while removing or vaporizing endometrial nodules. Five patients had partial vaginectomy and repair. In eight patients, the bowel was repaired via the laparoscope in one layer using interrupted 3-0 silk or 4-0 PDS (Ethicon) (Nezhat *et al.* 1991b). In the ninth, whose bowel was involved with endometriosis, laparoscopic anterior rectal wall resection and reanastomosis were performed after prolapsing the bowel via the anus (Nezhat *et al* 1991b). A patient in an earlier year underwent laparotomy for severe bowel stricture and was discharged on the fourth postoperative day (Nezhat *et al.* 1989c).

Ten patients underwent left ureterolysis, three had bilateral ureterolysis and four right ureterolysis. Two patients with hydroureter and mild hydronephrosis required ureteric stents for 6 weeks. There were no major complications. Six patients experienced bleeding from the 5 mm lower abdominal incisions and this was controlled by bipolar electrocoagulator or by one figure-of-eight suture with Tevdek No.5 (Fall River, MD). Eleven patients also had presacral neurectomy (Nezhat & Nezhat 1992). Four had laparoscopic hysterectomy and bilateral salpingo-oophorectomy (Nezhat *et al.* 1991f; Nezhat *et al.* 1992a). Eight had unilateral oophorectomy and four had bilateral oophorectomy (Nezhat *et al* 1991f). Thirteen patients had an appendicectomy (Nezhat & Nezhat 1991a). Seventeen women underwent myomectomy to remove leiomyomas up to 7 cm in diameter. Minor complications were shoulder pain, abdominal wall ecchymosis, urine retention and dyschezia for 1–2 weeks. The post operative use of hormonal therapy is prescribed on a case-by-case basis.

**Table 1.** Pain relief after surgery in 174 women

| Pain relief | No of patients ($n$=174) |
|---|---|
| Moderate to complete after | |
| One procedure | 145 |
| Two procedures | 13 |
| Three procedures | 4 |
| Total | 162 |
| Persistent or worse | 12 |
| Subsequent surgery | |
| TAH/SO | 5 |
| TAH/SO/bowel resection | 2 |
| Bowel resection | 2 |
| Further medical treatment | 3 |

Abbreviations: TAH = Total abdominal hysterectomy, SO = salpingo-oophorectomy.

Eleven of the 185 patients were lost to follow-up. The remainder have been followed for 1–5 years. Thus far, 31 patients (16%) have undergone second-look laparoscopies for persistent or recurrent infertility or recurrent pain. Of these 31 women, 12 (38%) had complete healing of the rectovaginal septum with few filmy adhesions; one in this group had persistent endometriosis. Nineteen (61%) had dense, vascular adhesions and seven in this group had persistent endometriosis.

Moderate to complete pain relief was observed in 162 of the 174 patients (93%), with 13 (8%) of these requiring two procedures, and four requiring three procedures. Twelve (7%) had persistent or worse pain following surgery. Nine of these 12 underwent subsequent surgery (Table 1).

Out of 61 patients with infertility, five were lost to follow-up and 25 (41%) achieved pregnancy. Table 2 details the AFS scores (American Fertility Society 1985) and other factors affecting the women who achieved pregnancy after surgery.

## Discussion

This report describes a special group of women with advanced endometriosis that is difficult to treat by conventional medical or surgical means. Results regarding pain relief and fertility following videolaseroscopic treatment of all stages of endometriosis were reported previously (Nezhat *et al.* 1986; Nezhat *et al.* 1989abcd; Nezhat *et al.* 1991e). Pouch of Douglas nodularity and involvement of the rectum can cause attachment of the rectum to the posterior aspect of the vagina and cervix, and the lower portions of the ureters. These conditions are associated with scarring, do not respond to medical therapy and should be treated surgically in most instances. Laparoscopic resection and vaporization have the advantages of enhanced visualization and precise control, both critical when operating deep in the pelvis.

Martin (1988) has reported five cases in which a combined laparoscopic and vaginal approach was used for the excision of infiltrating endometriosis of the pouch of Douglas. Coronado *et al.* (1990) have reported their experience with the surgical management of symptomatic colorectal endometriosis by laparotomy and bowel resection. Most of these lesions can be treated adequately and safely by videolaseroscopy. Using the video monitor, the assistant can guide the surgeon in locating the disease in the pouch of Douglas and identify the rectum and vagina, thus minimizing rectal damage (Nezhat *et al.* 1989c; 1991e, 1989b, 1989d). By using a high-power $CO_2$ laser, the

**Table 2.** The severity of the endometriosis in the women treated laparoscopically

| AFS score* | No. of women | No of pregnancies | Other contributing factors |
|---|---|---|---|
| 10–40 | 19 | 14 (73%) | No tubal involvement |
| 40–110 | 30 | 10 (33%) | Tubal adhesions, 14 patients had one or more endometriomas |
| > 116 | 12 | 1(8%) | Tubal adhesions, previous laparotomies, nine patients had one or more endometriomas |
| Total | 61 | 25 (41%) | |

*American Fertility Society (1985).

surgeon can safely cut and vaporize hard nodules which are very difficult to treat with other lasers or other methods. An experienced laparoscopist who is familiar with endometriosis should be able to detect a nodule with the probe.

Diluted vasopressin, the laser and bipolar forceps adequately control bleeding in these patients. Cautious and patient dissection of severe fibrosis and infiltrating endometriosis will ensure complete removal of the disease down to the normal areolar tissue of the pararectal area or the muscularis of the bowel. Constant irrigation is necessary to remove debris and charcoal. Hydrodissection will help differentiate between fibrosis and normal areolar tissue. Thorough understanding of the pelvic anatomy is critical to avoid damage to the ureter or rectum. To obtain optimum results, especially with regard to pain relief, endometriosis must be completely vaporized or excised. We believe that if a significant portion of bowel is involved and deeply invaded, segmental bowel resection is necessary. All the patients must have preoperative bowel preparation in case of possible entry into the rectum, and be emotionally and physically prepared for possible laparotomy. The surgeon should advance his technique gradually to ensure that videolaparoscopy is used effectively and safely, without unnecessary complications. An inexperienced surgeon will have an unacceptable level of complications which would slow the progress of therapeutic laparoscopy.

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GYNAECOLOGY

# Cone biopsy: has endocervical sampling a role?

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**ABSTRACT**

**Objective** To investigate the sensitivity, specificity and predictive value of endocervical sampling in women with abnormal cervical smears.

**Design** A randomized study of two methods of endocervical sampling.

**Setting** Colposcopy clinic at Aberdeen Royal Infirmary.

**Subjects** 100 women with abnormal cervical smears selected for cone biopsy according to current colposcopy criteria.

**Interventions** 53 women were randomized to have endocervical sampling with the Kevorkian curette and 47 to have sampling with the Medscand endocervical brush.

**Main outcome measures** Cytology and histology results from endocervical sampling compared with cone biopsy histology.

**Results** The overall sensitivity of endocervical sampling was 56%, with a false negative rate of 44% and a negative predictive value of 26%.

**Conclusions** Endocervical sampling should not influence management when colposcopy is unsatisfactory.

The role of sampling the endocervical canal at colposcopy has been debated for many years (Talebian *et al.* 1977; Hatch *et al.* 1985). In the USA such sampling is mandatory and the results obtained help to determine further investigation (Hatch *et al.* 1985; Drescher *et al.* 1983). In contrast, British colposcopic practice relies on the strict adherence to guidelines which determine the choice between local conservative treatment (for example laser ablation or cold coagulation) and cone biopsy.

The criteria allowing the use of conservative methods are that the transformation zone (TZ) and any lesion should be entirely visible; there should be neither colposcopic nor cytological suspicion of invasive cancer and the colposcopic findings should be consistent with the smear results. If these criteria are not met then a cone biopsy is indicated.

Large loop excision of the transformation zone has been shown to be a satisfactory method of conservative treatment (Prendiville *et al.* 1989; Luesley *et al.* 1990) and may make some of the above criteria obsolete, but there is no evidence, as yet, that it can completely replace cone biopsy.

Endocervical sampling is not routine in British colposcopy practice, nor has a role for it been assessed. Recent reports, however, have suggested that the technique may be useful to reduce the number of cone biopsies in which no malign epithelium is found, allowing safe conservative management (Luesley *et al.* 1987; Lopes *et al.* 1989). There have been no randomized studies examining the predictive ability of such sampling.

The standard method of obtaining endocervical epithelium has been curettage with the Kevorkian curette, although cytology samples obtained with endocervical brushes have been shown to give similar results (Andersen *et al.* 1988).

This study was designed to invetigate the sensitivity, specificity and predictive value of endocervical sampling and to compare the two methods of sampling, brush and curette.

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## Subjects and methods

The study group was recruited from women attending the colposcopy clinic at Aberdeen Royal Infirmary between October 1989 and July 1990. All the women were examined by one of the six experienced colposcopists who conduct the clinic. In Aberdeen women are referred for colposcopy if a single smear has shown severe dyskaryosis, if there is persistent mild or moderate dyskaryosis, or if there is cytological suspicion of invasive cancer.

Once the colposcopist has decided that a cone biopsy was necessary, the woman was entered into the study and was randomized by selection of a sealed envelope containing instructions to sample the endocervix with either a Kevorkian curette or a Medscand endocervical brush. The sampling was performed at the colposcopy examination. Depending on the individual clinician's preference, either a laser or cold knife cut cone biopsy was done 4 weeks later.

Between October 1989 and July 1990, 100 women had a cone biopsy and all of them were entered in the study. The women ranged in age from 21 to 64 (mean 44·6) years. Fifty three women were referred after a single severely dyskaryotic smear, forty one had recurrent mild to moderate dyskaryosis, five had cytological suspicion of invasive squamous cancer and one had a smear suspicious of adenocarcinoma. The indication for cone biopsy in 75 women was an unsatisfactory colposcopic examination in which either part of the lesion or part of the transformation zone was in the endocervical canal, beyond the limits of colposcopic vision. In eight women repeated mild or moderate dyskaryosis was unexplained by colposcopy. Ten women had cytological or colposcopic evidence of invasive disease or of a glandular lesion, and in seven women the indication for cone biopsy was not given.

Fifty three women were randomized to have endocervical sampling with Kevorkian curette and 47 to have sampling with

**Table 1.** Cone biopsy results in 19 patients with inadequate endocervical samples

| Endocervical sample | Cone biopsy<br>Negative | CIN | Invasive | Total |
|---|---|---|---|---|
| Curettage | 2 | 13 | 0 | 15 |
| Brush | 0 | 4 | 0 | 4 |
| Total | | | | 19 |

the Medscand endocervical brush. Endocervical curettage samples were placed immediately in Formalin and brush specimens were spread on a glass slide and immediately fixed with 100% ethanol. Both the cytology (brush) and the curettage specimens were examined by the routine services. The cytopathologists and histopathologists were aware of the study, but there was no attempt to standardize reporting as we considered that the results obtained from the routine service would more accurately reflect the situation in pathology laboratories around the country.

As the cytology specimens were from the colposcopy clinic, the brush specimens were reported by cytopathologists. Curettings were fixed in paraffin wax and then cut into blocks and examined by the histopathologists examining the routine specimens for that day.

Cone biopsies were sectioned into at least 12 blocks for histological examination.

The mean time between sampling and cone biopsy was 30·2 (range 0–126) days. Twenty five women underwent laser cut cone biopsy and 75 had cold knife conisation.

*Analysis*

Sensitivity, defined as the ability of the test to give a positive result when the individual tested has the disease, was calculated as the number of true positives divided by the sum of true positives and false negatives (expressed as a percentage).

Specificity, defined as the ability of the test to give a negative result when the subject is free of disease, was calculated as the number of true negatives divided by the sum of false positives and true negatives, expressed as a percentage.

The false negative rate was calculated as the number of false negatives divided by the sum of false negatives and true positives, expressed as a percentage.

The negative predictive value of the test was calculated as the number of true negatives divided by the sum of true negatives and false negatives, expressed as a percentage. The positive predictive value was calculated as the number of true positives divided by the sum of true positives and false positives, expressed as a percentage.

**Table 2.** Comparison of cone biopsy and endocervical curettage histology

| Endocervical curettage | Cone biopsy<br>Negative | CIN | Invasive | Total |
|---|---|---|---|---|
| Negative | 5 | 12 | 0 | 17 |
| CIN | 1 | 16 | 5 | 22 |
| Invasive | 0 | 0 | 0 | 0 |
| Total | 6 | 28 | 5 | 39 |

**Table 3.** Comparison of cone biopsy histology with endocervical brush cytology

| Endocervical brush | Cone biopsy<br>Negative | CIN | Invasive | Total |
|---|---|---|---|---|
| Negative | 4 | 14 | 1 | 20 |
| CIN | 3 | 17 | 2 | 22 |
| Invasive | 0 | 1 | 0 | 1 |
| Total | 7 | 32 | 3 | 42 |

A negative sample was defined as a sample which contained no malign epithelium, considered satisfactory for reporting.

A false negative result was one where the endocervical sampling contained no malign material and the cone biopsy showed either cervical intraepithelial neoplasia (CIN) or cancer. Sampling results showing CIN where the cone contained cancer were not considered false negatives.

## Results

Of the 100 samples taken, 19 (19%) were unsatisfactory, with insufficient cellular material for cytological examination (Table 1).

Fifteen cone biopsies had no abnormality, 77 showed CIN (65 CIN 3, 11 CIN 2, 1 CIN 1). There were five micro-invasive and three invasive (Stage 1b) squamous cancers.

Table 2 compares the histology from endocervical curettage and cone biopsy. Table 3 compares endocervical brush cytology and cone biopsy histology. Table 4 compares the results of endocervical sampling by both techniques with the cone biopsy histology. From these tables it can be seen that there was complete agreement between endocervical sampling and cone biopsy in only 50% of cases (considering only samples satisfactory for reporting).

The sensitivities of curettage and brush cytology sampling methods were 57% and 53%, respectively and the combined sensitivity for endocervical sampling was 56%. The specificity was calculated as 69%, but the accuracy of this figure is doubtful because of the small numbers involved.

The false negative rate for curettage was 46% (12 cases) and for brush cytology was 45% (15 cases). The total false negative rate for endocervical sampling was 44.3% (27 cases). The predictive value of both a positive and a negative sampling result are shown in Table 5.

**Table 4.** Comparison of cone biopsy histology with results of endocervical sampling by endocervical curettage or endocervical brush

| Endocervical sampling | Cone biopsy histology<br>Negative | CIN | Invasive | Total |
|---|---|---|---|---|
| Negative | 9 | 26 | 1 | 36 |
| CIN | 4 | 33 | 7 | 44 |
| Invasive | 0 | 1 | 0 | 1 |
| Total | 13 | 60 | 8 | 81 |

**Table 5.** Predictive values and false negative rates of endocervical sampling

| Endocervical sampling | Positive predictive value (%) | Negative predictive value (%) | False negative rate (%) |
|---|---|---|---|
| Curettage | 94 | 29 | 43 |
| Brush | 85 | 22 | 45 |
| Both methods | 89 | 26 | 44 |

## Discussion

Whether or not endocervical sampling should be performed at all colposcopy examinations is a contentious issue; but there are no reports on the value of the methods employed for such sampling. Most studies have either examined few women (Sesti *et al.* 1990), or have been retrospective assessments of women with both satisfactory and unsatisfactory colposcopies where the final histology result was either punch biopsy or cone biopsy, or women diagnosed as having CIN on punch biopsy then having a destructive local treatment (Hatch *et al.* 1985; Drescher *et al.* 1983; Krebs *et al.* 1987). In some cases no histology was available.

There is no information on the value of a negative endocervical sampling or whether a negative result should influence management, particularly when the colposcopy is unsatisfactory. Our study shows that the two recognized methods of obtaining samples from the endocervix have a high false negative rate (44%), and a correspondingly low ability to predict freedom from disease (26% negative predictive value). The tests do not facilitate management when colposcopy is unsatisfactory: the endocervical sampling missed significant CIN and an invasive cancer. The value of endocervical sampling for avoiding negative cone biopsy, as suggested by Lopes *et al.* (1989), is dubious.

More than 75% of the women in our study required cone biopsy because the lesion was in the canal or because the transformation zone was not entirely visible. It is, therefore, unlikely that the false negative results were due to lesions being missed because they were entirely ectocervical. Indeed, it has been demonstrated that endocervical curettings in such cases are usually contaminated by the ectocervical lesion and show up as positive (Spirtos *et al.* 1987).

Our study has demonstrated that endocervical sampling should not influence management when colposcopy is unsatisfactory. The information may be incomplete if CIN is found and the result is unreliable when negative.

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CLINICAL PRACTICE

# 25 mg oestradiol implants—the dosage of first choice for subcutaneous oestrogen replacement therapy?

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**ABSTRACT**

**Objective** To assess the oestrogen concentrations and symptom relief obtained with 25 mg oestradiol implants.

**Design** Open, observational study.

**Subjects** Twelve symptomatic, post-menopausal women seen in a designated menopause clinic.

**Intervention** A 25 mg oestradiol pellet was inserted subcutaneously, blood samples were obtained before implantation and at regular intervals (2–4 weeks) until symptoms refused as hypoestrogenaemia developed.

**Main outcome measures** Change in symptom score following implant treatment. Concentrations of oestrogens and their metabolites before and during low dose subcutaneous oestradiol therapy.

**Results** Ten of the 12 women had excellent symptom relief, associated with oestradiol concentrations in the follicular range for between 28 and 35 weeks. The ratio of circulating oestrogen metabolites remained physiological, despite the oestradiol concentrations being substantially higher on treatment.

**Conclusions** We suggest that 25 mg pellets should be used as the initial dose for subcutaneous oestrogen treatment, and a combination of return of symptoms and weeks since insertion used to judge the timing of reimplantation.

In the United Kingdom there are nearly ten million postmenopausal women (Office of Population Censuses and Surveys 1990) and the use of hormone replacement therapy is increasing in this group as more women recognize that symptoms due to oestrogen deficiency can easily be treated. The oral route of administration of oestrogens is cheap and provides effective therapy for climacteric problems, but because relatively large doses of oral oestrogens are required to produce plasma oestradiol concentrations within the physiological range, adverse symptoms and detrimental hepatic effects may result (Coope *et al.* 1975; Geola *et al.* 1980; Helgason 1982; Lobo 1980; Notelovitz 1987; Von Schoultz 1988).

Percutaneous and subcutaneous methods of administration avoid these high portal vein concentrations and are thus considered safer in certain circumstances, for example in women with a past history of hepatic or clotting dysfunction. The most commonly used oestradiol implants are 50 mg and 100 mg and these, particularly with repeated usage, may lead to supraphysiological oestradiol concentrations, a source of anxiety and potential side effects (Barlow *et al.* 1986; Barlow 1988; Eden 1988; Ganger *et al.* 1989; Swyer 1989). On the principle of prescribing the lowest dose of a drug necessary for appropriate symptom relief, we wished to investigate the efficacy and duration of action of the lower dose 25 mg oestradiol implant.

There are several reports of effective relief of symptoms with this dose of subcutaneous oestradiol (Staland 1978; Greenblatt *et al.* 1979; Kapetanakis *et al.* 1982; Notelovitz *et al.* 1987) but few pharmacokinetic data are available and there are no published data on the use of 25 mg oestradiol implants in the United Kingdom. Oestradiol ($E_2$) is principally metabolized to oestrone, which in turn is conjugated with sulphate and glucuronide. The glucuronides enter the enterohepatic circulation and are rapidly cleared by the kidney and contribute most of the excreted oestrogen. Oestrone sulphate, on the other hand, is metabolized very slowly and thus forms a large pool of what is generally considered to be inactive oestrogen. Sulphates and glucuronides of oestradiol and oestriol are also present in the circulation but in much lower concentrations than the oestrone conjugates.

The profile of plasma oestrogen metabolites varies with the route of administration, for example, after gut absorption the subsequent hepatic breakdown results in a disproportionate rise in oestrone and oestrone sulphate (Selby *et al.* 1989). As there are no published data on the metabolic profiles associated with the subcutaneous route of administration, we wished to study the concentrations of oestrone, oestradiol and their glucuronides and sulphates after implant therapy.

## Subjects and methods

Twelve symptomatic, postmenopausal women were recruited for this open, observational study, from new referrals to a des-

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ignated menopause clinic. The study had local ethics committee approval and all women signed a detailed consent form. All of the women were hypergonadotrophic (follicle stimulating hormone >35 iu/l), hypoestrogenic ($E_2$ <100 pmol/l) and were complaining of hot flushes with or without other symptoms. Their ages ranged from 35 to 63 years and they had experienced a spontaneous, or in two cases surgical, ovarian failure between 6 months and 10 years earlier (median 2 years). The women had body mass indices ranging from 19 to 29 kg/m$^2$ and none of them had any contraindication to oestrogen therapy.

At entry into the study the women completed a modified 'Kupperman' questionnaire (Kupperman *et al* 1953)—an 11 point self-assessment symptom questionnaire. The symptoms enquired about included hot flushes, numbness or tingling in the hands or feet, difficulty sleeping, nervousness and sadness, dizziness and tiredness, headaches and pains in the joints or muscles, palpitations and formication. The women scored the severity of their symptoms from 0–3 corresponding to 'not at all', 'mild', 'moderate' or 'severe' with weighting of four-fold for the severity of the hot flushes and two-fold for the subsequent three symptoms. The maximum possible score was thus 51.

A 25 mg oestradiol pellet was inserted subcutaneously, under local anaesthesia, in the buttock or lower abdomen (Greenblatt *et al* 1949; Thom & Studd 1980). The implant used was the standard fused crystalline 17β-oestradiol preparation, 2·2 mm in diameter (Organon Laboratories, Cambridge, UK). Because of the small size of the implant, and thus the small size of the trocar, a suture was not required. All women were given oral dydrogesterone (Duphaston, Duphar Laboratories, Southampton, UK), 10 mg daily, for 12 days, from the first day of the calendar month.

The Kupperman questionnaire was completed and blood sample was obtained baseline, 2 weeks and 4 weeks after the implant and then every 4 weeks until 20 weeks after the treatment, or sooner, if symptoms returned. Subsequently, the women were seen every 2 weeks until they completed the study. The blood was spun and the serum stored at –20°C. The study was completed when symptoms recurred, as assessed by a substantial increase in the symptom score, or when the $E_2$ concentrations returned into the menopausal range. The serum was analyzed for oestrone, oestradiol and oestriol and their sulphate and glucuronide conjugates as described previously (Selby *et al.* 1989). The intra-assay variations ranged from 9·1 to 15·8%.

### *Data presentation*

The serum concentrations and symptom scores are presented as medians and individual results, as the data were not normally distributed and the numbers were small (Gardner & Altman 1989). The week of implantation was designated week 0 and the symptom scores during the study were expressed as a percentage of the initial score, due to the wide variation between the women. In the figures, the data are grouped into 2-, 4- and then 2-week intervals. The 'area under the curve' for the oestradiol concentrations over time is presented for the 10 women who continued after 15 weeks (Matthews *et al* 1990).

### *Statistical analysis*

Linear regression analysis was performed on the $E_2$ concentrations and symptom scores. Wilcoxon's signed rank test was performed on the paired results of pre- and post-implant oestrogen (and metabolites) concentrations.

## Results

All the women had an increase in serum oestradiol concentrations and relief of symptoms by 2 weeks after implantation. One woman was withdrawn from the study at 20 weeks because she developed symptoms from a benign brain tumour. Another woman required reimplantation after 16 weeks because of the return of symptoms in the presence of low serum oestradiol concentrations, but the other 10 women continued in the study for a median of 29 weeks (range 28–35) after implantation

The change in symptom score over time in all 12 women is shown in Fig. 1. Symptoms decreased in all the women within the first 2 weeks. The median reduction in symptom score was 60%. Excluding the women who required another implant after 16 weeks and the woman with the brain tumour, further treatment was not required until at least 26 weeks after implantation (median 29 weeks, range 26–35 weeks).

The change in serum oestradiol concentrations during the treatment period is shown in Fig. 2. By 2 weeks after implantation, the median serum oestradiol concentrations was 377 pmol/l, with a four fold variation between the highest and the lowest concentrations (190–782 pmol/l). After 3 months the intersubject variation had narrowed and oestradiol concentrations remained at early to mid follicular phase levels until the end of the study. Analyzing the 'area under the curve' for the oestradiol concentrations over the period of the study, the results are all within the physiological range (Fig. 3), and with less intersubject variation (approximately 2·5 fold).

There was no correlation between oestradiol concentrations and symptom relief in the overall group (data not shown). Rapid return of symptoms, associated with a decrease in the oestradiol concentration to 175 pmol/l, was noted in one woman at 14 weeks. In the other women the return of symptoms was associated with higher oestradiol concentrations than their initial values (range 340 n 182 pmol/l) and no threshold level could be defined.

Oestradiol concentrations exceeded oestrone concentrations

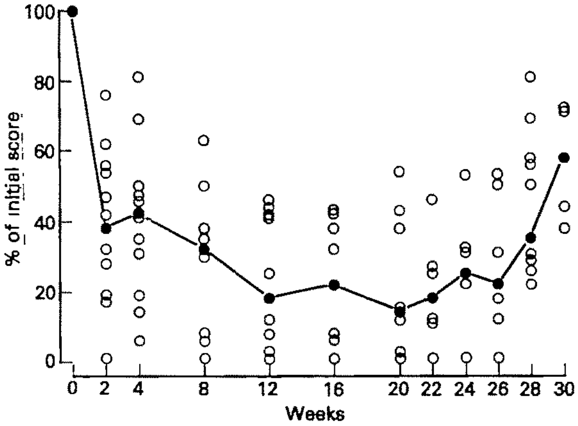

**Fig. 1.** Change in symptom score following 25 mg oestradiol implantation at week 0. Results are shown as a percentage of the initial (pre-implantation) score ●——●, median

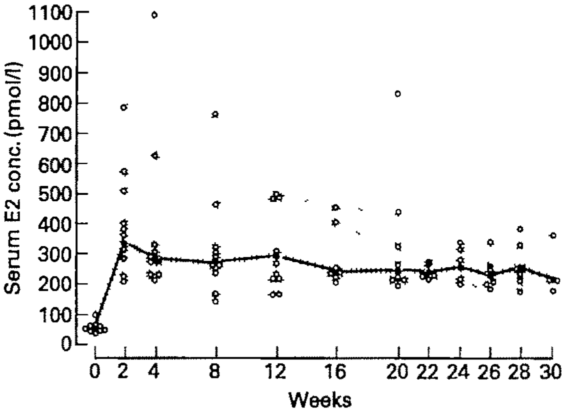

**Fig. 2.** Serum oestradiol ($E_2$) concentrations following 25 mg $E_2$ implantation at week 0. The shaded area highlights the range (excluding one result at week 20–21). ●——●, median.

in all women after treatment, with the oestradiol/oestrone ratio reversing from a median of 0·56 at baseline to 1·5 at 2 weeks and thereafter. Fig. 4 demonstrates the changes in the various oestrogen metabolites 8 weeks after the 25 mg oestradiol implant. Before treatment, oestrone sulphate concentrations predominated with very low concentrations of the other oestrogens fractions. At 8 weeks after implantation the median concentrations of oestradiol and all the metabolites (except oestriol glucuronide) had risen substantially but the ratios were similar to pretreatment. The main metabolite, oestrone sulphate, was still in the highest concentration in the serum, but the oestradiol concentration was disproportionately higher.

## Discussion

In this group of 12 unselected women the efficacy of low dose oestradiol implants has been clearly demonstrated, although larger studies to corroborate these results would be valuable. The fact that 10 of the 11 women, who were able to complete the study, had symptom relief for over 6 months confirms that use of this implant dose is realistic. The oestradiol concentrations achieved were within the early follicular range in most women, although there was considerable variation between women. This suggests that the higher concentrations achieved with the 50 mg and 100 mg implants are unnecessary for control of symptoms. The variation between individuals was greater in the first 3 months than subsequently, being four to five fold between the lowest and the highest. Taking the whole period of the study, however, there was less intersubject variability in oestradiol concentrations, as represented by the 'areas under the curve'. We were unable to establish the reasons for the intersubject differences, as the oestrogen profiles did not show any consistent patterns that could be associated with altered absorption or metabolism; neither could these differences be explained by variation in body mass index.

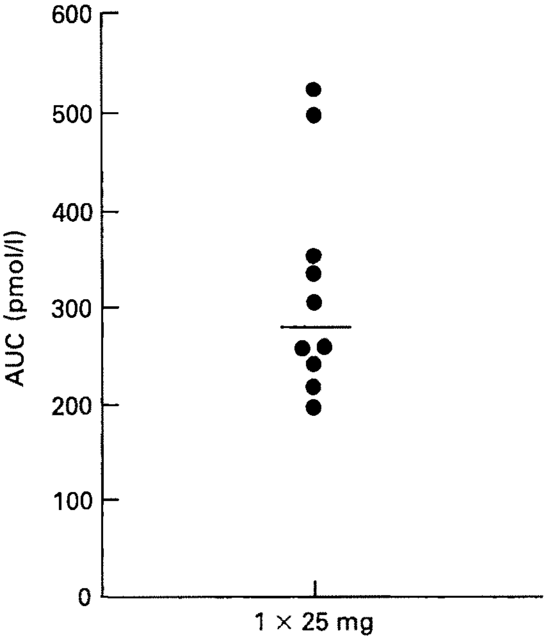

**Fig. 3.** Individual 'areas under the curve' (AUC) for oestradiol concentrations over the time period of the study using a single 25 mg oestradiol implant. The horizontal bar represents the median result.

In practice, however, the differences in circulating oestradiol concentrations with this dose of implant were narrow compared with those seen after oral administration, where five to ten fold variations are seen (Akpoviroro & Fotherby 1980), and also showed less variation than with the 50 or 100 mg pellets (Thom *et al.* 1981). With these higher doses of implants there is a greater differential between peak and trough values and a declining mean value in the months following implantation. This is clinically important as falling concentrations seem to provoke symptom return (Thom & Studd 1980; Barlow 1988; Cardozo *et al* 1984). This has been described as tachyphylaxis but this is probably not an appropriate example of that phenomenon. Tachyphylaxis usually describes a reduced physiological response to a standard dose of drug. In the situation found with high dose oestradiol implants, however, the problem is the return of symptoms in the presence of supraphysiological concentrations of oestrogen. This may be due to a relative change in oestradiol concentrations, or to decreases below a threshold level. We did not find this problem with the 25 mg dose.

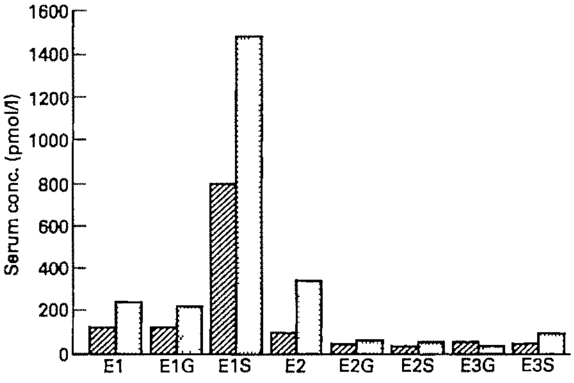

**Fig. 4.** Median serum levels of oestrogens and their metabolites in 12 postmenopausal women before treatment (▨) and 8 weeks after treatment with 25 mg oestradiol implant (□). All changes were significant ($P$ = <0·01) except the oestriol metabolites.

$E_1$ = Oestrone; $E_2$ = Oestradiol; $E_3$ = Oestriol; S = Sulphate; G = Glucuronide.

We were, however, unable to correlate the return of symptoms with serum oestradiol concentrations. Despite maintaining concentrations well above pretreatment values until the end of the study, all women eventually complained of worsening of symptoms. Whether this was an effect of the aforementioned change in the concentrations of oestradiol, or one of the other metabolites, could not be established. Return of symptoms was not an accurate guide to absolute oestradiol concentrations, but using a 25 mg implant the women were unlikely to develop very high concentrations with repeated implants. We suggest, therefore, that the timing of reimplantation be judged by a combination of symptom recurrence and time since insertion. If, however, rapid return of symptoms were to occur, measurement of oestradiol concentration could differentiate between symptom return due to hypoestrogenaemia and that adequate (or high) oestradiol concentrations, where reimplantation may be inappropriate.

We have demonstrated that the absorption of $E_2$ from the subcutaneous site of implantation leads to a more physiological profile of circulating oestrogens than that seen with oral administration, and similar to that seen with the transdermal route of absorption (Selby *et al.* 1989). The implant does, however, avoid the inconvenience of twice weekly change of patches and the development of adverse skin reactions. Although there are no data suggesting that altered ratios of the metabolites are deleterious per se, the very high concentrations of oestrone sulphate seen with oral administration may be better avoided.

The main indication for hormone replacement therapy is symptom relief. This dose is effective. It may be that supraphysiological replacement will be important in certain situations; for example the augmentation of bone density in established osteoporosis, but this is unlikely to be needed for the majority of women. Savvas *et al.* (1988) have suggested that where low concentrations of oestrogen replacement are provided orally, bone mineralization may not be preserved. A 'threshold level' has not, however, been established and when treating prophylactically repeated bone densitometry may be needed to confirm the individual effect rather than a population effect. Preliminary studies on the oestradiol patches suggest that $E_2$ concentrations similar to those found in this study may be adequate to maintain bone mass (Stevenson *et al* 1990), and Notelovitz *et al.* (1987) found no change in bone mineral density in the radius of six women using the 25 mg implant.

The risk to the endometrium of unopposed oestrogens is not lessened because the woman delays her next implant. Progestogens must be administered to all women with an intact uterus and should be continued until the oestradiol concentrations fall within the menopausal range of until there are no further withdrawal bleeds. We used dydrogesterone because it is a non-androgenic progestrogen that is also effective in producing secretory change in the endometrium (Siddle *et al* 1990).

The use of 25 mg implants as treatment for menopausal symptoms of many women could be easily managed by their general practitioner, with the minimum of equipment, and very little risk of overdosing. The oestradiol concentrations remain in the physiological range in many women for far longer than was appreciated previously.

We have demonstrated that the efficacy and duration of action of the 25 mg implant is greater than was commonly thought. Because of this and the ease of insertion of the smaller 25 mg pellet, we believe that this is the most appropriate starting dose for most women. We suggest that a combination of return of symptoms and measurement of $E_2$ concentrations be used to determine when best to reimplant.

## Acknowledgments

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FERTILITY CONTROL

# Genital tract infections associated with the intrauterine contraceptive device can be reduced by inserting the threads into the uterine cavity

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**ABSTRACT**

**Objective** To study the influence of the position of the threads of an intrauterine contraceptive device (IUCD) on the development of genital tract infection.
**Design** A multicentre randomized controlled trial.
**Subjects** Women requesting an IUCD.
**Interventions** The women were randomized to be fitted with an IUCD either with the threads contained in the uterine cavity (threads-up group) ($n = 208$) or passing through the cervix to the vagina in the usual way (threads-down group) ($n = 237$). Multiple centre study with follow-up at three months, 1 and 2 years. At the final visit 'missing' threads were retrieved using a disposable instrument (Retrievette$^R$).
**Main outcome measures** The occurrence of infection in the lower or upper genital tract.
**Results** 63 women in the threads-up group and 78 in the threads-down groups dropped out. Previous gynaecological infection was reported by 21 and 48 women in the threads-up and threads-down group, respectively (odds ratio 0·44, 95% CI 0·24 to 0·79), 21 and 53 subjects had signs of infection at gynaecological examination (odds ratio 0·39, 95% CI 0·21 to 0·69) and a wet-smear was pathological in 33 and 79 (odds ratio 0·38, 95% CI 0·23 to 0·61). In the threads-up group the vaginal pH was also lower at the final check up after 2 years. Spontaneous descent of the threads occurred in 11% of the threads-up group and in six women in the threads-down group the threads were in the cervix. In 93 women the threads were easily retrieved by means of the Retrievette$^R$, four women insisted on the threads remaining in the uterus and in 18 thread removal was performed under local or general anaesthesia.
**Conclusions** Infectious complications in women using an IUCD are more frequent if the threads lead from the uterine cavity to the vagina. This problem can be reduced by inserting the threads so that they remain entirely within the uterine cavity, a feasible procedure now that an effective instrument for IUCD thread retrieval is available.

The risk of developing pelvic inflammatory disease (PID) is increased in women using an intrauterine contraceptive device (IUCD) and, this is particularly true for younger women with more than one sexual partner (Burkman *et al.* 1981; Eschenbach *et al.* 1980; WHO report 1987). It has been assumed that bacteria can follow the strings of an IUCD into the uterine cavity and then invade the fallopian tubes, but clinical studies have been conflicting (Tatum *et al.* 1976; Sparks *et al.* 1980; Jacques *et al* 1986). We have investigated the role of the IUCD threads in a randomized trial comparing conventional insertion with the insertion of the threads along with the device into the uterine cavity. The results at 3 months for some of the women of this study have been published earlier (Pap-Åkeson *et al.* 1989) and we now report the full 2 years of follow-up.

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## Subjects and methods

A total of 445 women at three family planning clinics, who requested an IUCD for contraception were included in a uniformly monitored, multicentre study. The planned size (2 × 250 participants) of the study was sufficient to demonstrate a significant difference between the treatment groups with respect to the probability of infection provided that the observed probability in the treated group was reduced from 0·25 to 0·15. The age range was 20–47 years and four women were nulliparous. The time since the last pregnancy varied between 3 months and 22 years. The exclusion criteria for the study included a history of previous salpingitis or ectopic pregnancy, ongoing pregnancy, symptoms or signs of genital infection and irregular bleeding. The study was approved by the local ethics committees and informed consent was obtained from all participating women.

**Table 1.** Characteristics of the women in the two study groups

| Characteristic | Threads-up (*n* = 208) | Threads-down (*n* = 237) |
|---|---|---|
| Age (years) | 33·3 (6·4) | 33·1 (6·3) |
| Number of previous pregnancies | | |
| 0–1 | 38 | 48 |
| 2–3 | 161 | 183 |
| 4+ | 9 | 5 |
| Length of uterine cavity (cm) | 7·7 (0·9) | 7·6 (0·8) |
| Previous contraception | | |
| None | 58 | 67 |
| IUCD | 66 | 78 |
| Oral contraceptive | 28 | 31 |
| Other | 56 | 60 |
| Unknown | | 1 |

Results are mean (SD) values or number of women as appropriate.

At the first visit a history was taken and a gynaecological examination was performed. Samples were obtained for a chlamydia test or culture, a 'wet-smear' was examined (Larsson & Platz-Christensen 1990) and the pH of the vaginal fluid was determined. The women were then fitted with a Multiload Cu 250$^R$ IUCD (Organon AB, Sweden) and were randomized (using sealed envelopes) either to have the threads inserted into the cavity together with the device (threads-up group) (*n* = 208) or fitted in the traditional way with threads leading into the vagina (threads-down group) (*n* = 237). In the former group, the device was first taken out of the insertion tube under sterile conditions, the threads cut to a length of 5 cm and the IUCD replaced in the tube, but with the threads upwards in parallel with the IUCD. Age groups 20–29, 30–39 and 40–47 were randomized separately in order to avoid unequal distribution between study groups.

Follow-up examinations were made at 3 months, 1 year and 2 years. At each visit the women were questioned about possible genital tract infections, bleeding disturbances (prolonged periods or intermenstrual bleeding), and other relevant symptoms. A gynaecological examination was performed, which again included examination of a wet-smear, and the measurement of the vaginal pH. Clinical evidence of infection at gynaecological examination was defined as a foul-smelling discharge with or without tenderness of the uterus and adnexae. Whenever symptoms or signs of infection were present, investigation for chlamydia was performed. At the 3-month check-up in the threads-up group the device was localized ultrasonically.

In the threads-up group, at the final check-up at 2 years, the threads were brought down into the vagina. For this purpose, after checking that the threads were not already in the cervical canal, a specific disposible instrument for thread retrieval (Retrievette$^R$) was used (Pap de Pestény *et al.* 1986); if this was unsuccessful, further measures were employed. The women's immediate discomfort at the time of thread retrieval was noted and a postal questionnaire was sent after an interval of 1–2 months to detect late symptoms.

Comparisons between the treatment groups were performed by Fisher's permutation test (Bradley 1968), which includes Fisher's exact test as a special case. All tests were two-sided. Odds ratios were estimated and 95% confidence intervals (CI) were determined (Lehmann 1959).

## Results

At the time of insertion no differences between the groups were found in age, number of previous pregnancies, the length of the uterine cavity or previous contraception (Table 1). Chlamydia were detected in six women in the threads-up group and in seven in the threads-down group, all infections were asymptomatic. These women were treated with tetracyclines with the IUCD still in place and remained free of signs and symptoms.

At the 3 months ultrasound follow-up, all but one of the women in the threads-up group still had the IUCD correctly placed in the uterine cavity. These women accepted not being able to feel the strings of the device themselves.

A total of 141 women withdrew during the two years of the study for reasons that are shown in Table 2. The number who withdrew because of symptoms and signs of infection in the threads-up group was significantly lower than in the threads-down group. Among the withdrawals were five women with intrauterine and two with ectopic pregnancies.

Histories of infection, bleeding disturbances and signs of infection in all women, as well as in those remaining in the

**Table 2.** Reason for withdrawal from the study

| Reasons for withdrawal | Threads up group (*n* = 208) | Threads down group (*n* = 237) | Odds ratio | (95% CI) |
|---|---|---|---|---|
| Medical | | | | |
| Bleeding disturbances | 19 | 25 | 0·85 | (0·43 to 1·67) |
| Foul-smelling discharge or other symptoms and signs of infection | 2 | 12 | 0·18 | (0·05 to 0·82)* |
| Pain | 2 | 5 | 0·45 | (0·08 to 2·78) |
| Intrauterine pregnancy | 4 | 1 | | |
| Ectopic pregnancy | 1 | 1 | | |
| Social | | | | |
| Lost to follow-up | 13 | 9 | 1·69 | (0·65 to 4·56) |
| Wish to become pregnant | 9 | 15 | 0·67 | (0·25 to 1·66) |
| Other causes | 13 | 9 | 1·69 | (0·65 to 4·56) |
| | 63 | 78 | | |

*$P$<0·05

**Table 3.** Symptoms and signs of infection throughout 2 years of study in women in whom an IUCD was inserted together with the threads and those fitted with an IUCD in the traditional way

| Symptoms/ signs | Threads-up group ($n$ = 208 (145)) | Threads-down group ($n$ = 237 (157)) | Odds ratio | (95% CI) | Probability |
|---|---|---|---|---|---|
| History of gynaecological infection* | 21 (7) | 48 (26) | 0·44 | (0·24 to 0·79) | $P$<0·01 (=) |
| Bleeding disturbance | 57 (50) | 75 (49) | 0·82 | (0·53 to 1·25) | (ns) |
| Sign of infection at gynaecological examination | 21 (5) | 53 (26) | 0·39 | (0·21 to 0·69) | $P$<0·01 (=) |
| Pathological wet-smear | 33 (12) | 79 (49) | 0·38 | (0·23 to 0·61) | $P$<0·01 (=) |
| pH (mean ± SD) of vaginal content | 4·86 (0·59)<br>[4·84 (0·60)] | 4·97 (0·59)<br>[4·97 (0·63)] | | | ns ($P$<0·01) |

*The types of infection in the 'threads-up' and 'threads-down' groups in the women still remaining in the study after 2 years were: salpingitis 0/3, endometritis 1/5, lower genital tract infection 5/14 and other infections 1/4, respectively.

The number in parenthesis shows the number of women remaining in the study after 2 years; statistical comparisons are based on the groups as originally allocated and includes the drop-outs

study at the final check-up after 2 years of IUCD use, are shown in Table 3. In the threads-up group significantly fewer women gave a history of gynaecological infection, had signs of infection on gynaecological investigation or had pathological wet smears; none had had salpingitis and only one had had endometritis. Considering only the women remaining in the study at the final examination those in the threads-up group had a lower vaginal pH.

At the final check-up after 2 years, spontaneous passage through the cervix of the threads had occurred in 24 women in the threads-up group, whereas threads were not seen in the cervical os in seven of the women in the threads-down group; in six of these women the threads were seen in the cervical canal and the IUCDs were withdrawn using a Spencer-Wells forceps. Successful extraction of threads from the uterus was performed in 93 of the women using the Retrievette$^R$ instrument; four women insisted in keeping their IUCD threads in the uterine cavity. The retrieval procedure with the special instrument was unsuccessful in 18 women, in whom the threads had to be brought down under local or general anaesthesia. This lack of success was due to discomfort in 15, aberrant anatomy in two and instrument failure in one.

The women's immediate experience of the IUCD thread retrieval procedure with the Retrievette$^R$ is shown in Table 4. Only 13 described their discomfort at withdrawal as considerable and, in general, the pain was about the same as at insertion. From the questionnaire completed 1–2 months later, it was found that none of the women had developed any protracted bleeding or signs of pelvic infection after thread retrieval, although one had had a vulvo-vaginitis due to *Candida albicans*.

## Discussion

In the present study, there was less gynaecological infection in the threads-up group and at the final examination pH of the vaginal content was lower. Among serious infections in the threads-down group were three women with salpingitis and five with endometritis, whereas endometritis occurred in only one of the women of the threads-up group. However, the overall occurrence of severe infection, including positive chlamydia tests or cultures, was low in the women studied, illustrating the importance of appropriate selection of women for IUCD use. Most of the infections were confined to the lower genital tract, so-called bacterial or *Candida albicans* vaginosis.

Bacteriological studies indicate that the uterine cavity is usually sterile (Ansbacher *et al.* 1967; Sparks *et al.* 1977), but that insertion of an IUCD can cause contamination with the bacteria normally found in the vagina and lower cervix (Mishell *et al.* 1966). Bacteria tend to disappear within the first weeks after IUCD insertion, but in some instances they adhere to the endometrium and, to a lesser degree, to the device itself, thereby remaining longer in the uterus. IUCD strings can interfere with the cervical barrier, thereby providing a lead for bacterial growth (Sparks *et al.* 1979). In such cases bacteria can remain in the uterine cavity for several months (El Kholi *et al.* 1977).

Some earlier clinical studies found no significant differences in PID rates between women using an IUCD with or without monofilament threads leading out through the cervix (Willson *et al.* 1965; Buchman 1970; Tietze & Lewit 1970; Burnhill 1973). Explanations for this could be that the criteria for diagnosing PID differed between various centres or that the populations studied were too small to establish significant differences, because of the low frequency of PID. The latter was probably also the case in a more recent study from Guatemala involving a total of 300 women with IUCDs with and without threads, with only five with PID and no statistically significant differences between the groups (Galvez *et al.* 1985). In contrast, Elstein *et al.* (1967) reported a much higher incidence of PID in women with the tailed Lippes' loop than with the Birnberg bow without tails. A French prospective study of 84 women (Cohen 1987) with a Copper-T 200 with or without threads had no cases of PID, but the rate of lower geni-

**Table 4.** Discomfort experienced during IUCD thread retrieval by the Retrievette$^R$ instrument ($n$ = 145) after 2 years of use of an IUCD which had been inserted with the threads together with the device into the uterine cavity

| Discomfort | | In comparison to the IUCD-insertion | |
|---|---|---|---|
| Considerable | 13 | More | 26 |
| Moderate | 47 | The same | 29 |
| Little | 40 | Less | 39 |
| No report | 11 | No report | 17 |

tal tract infection in that study was 24% in the string group and 12% in the group without strings. A comparative clinical study from Hungary and Finland with about 600 cases with and 600 without tails on their IUDs (Batar *et al.* 1988) showed a cumulative termination rate after 24 months which was the same in the two groups for bleeding, pain, planned pregnancy and other clinical reasons. Only removal because of PID differed statistically between the two groups, with 11 devices with tails taken out compared with only one fitted without thread.

The present data confirm that not only multifilament but also the monofilament threads of modern devices can convey infection through the cervix and into the uterus. This study shows that the problem of infection can be markedly reduced by inserting the threads together with the IUCD from the beginning, now that a feasible method for safe thread retrieval is available (Pap de Pestény *et al.* 1986; Bounds *et al.* 1992). To confirm the causative role of the IUCD threads in ascending uterine infections, we have started a histopathological and bacteriological study of women undergoing hysterectomy after the insertion of an IUCD with threads positioned the traditional way or along with the device in the uterus.

## Acknowledgments

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FERTILITY CONTROL

# Stimulation of vasopressin release in women with primary dysmenorrhoea and after oral contraceptive treatment—effect on uterine contractility

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## ABSTRACT

**Objective** To study aspects of the aetiology of primary dysmenorrhoea and mechanisms underlying the therapeutic effect in this condition of an oral contraceptive.

**Intervention** Intrauterine pressure was recorded before and during infusion of hypertonic saline (5% NaCl, 0·06 ml/kg/min) over 75 min on the first day of bleeding in women with dysmenorrhoea and after 3 weeks of oral contraceptive treatment. Plasma sampling every 15 min of ongoing infusion for the estimation of osmolality, arginine vasopressin, oxytocin and the prostaglandin (PG) F-metabolite, 15-keto-13,14-dihydro-PGF$_{2\alpha}$.

**Subjects** Ten healthy nulliparous women with moderate to severe primary dysmenorrhoea.

**Main outcome measures** Plasma levels of posterior pituitary hormones and the PGF-metabolite. Total pressure area (TPA) of the recording curve.

**Results** In dysmenorrhoea before infusion the plasma concentration of vasopressin was in mean 2·18, oxytocin 5·05 and the PGF-metabolite 321·5 pmol/l, and the TPA 3·8 kPa × 10 min. After oral contraceptive treatment the vasopressin level and the TPA were significantly reduced. At both sessions apart from intensifying the pain, the saline infusion increased vasopressin and oxytocin levels as well as the TPA, whereas the concentration of the PGF-metabolite at both sessions decreased.

**Conclusion** Confirmation is provided of the elevated secretion of arginine vasopressin and PGF$_{2\alpha}$, as well as increased uterine activity in primary dysmenorrhoea. The observations are in agreement with the concept that a lowered level of vasopressin and a decreased uterine activity contributes to the beneficial effect of OCs in the condition. Stimulation of the secretion of vasopressin increases the uterine activity and symptoms of primary dysmenorrhoea, but results suggest that this effect does not involve a mechanism of increased PGF-synthesis. The role of oxytocin in dysmenorrhoea can not yet be defined.

In women with primary dysmenorrhoea we have demonstrated previously an increased level of arginine vasopressin, a hormone which may cause increased uterine contractility and reduced blood flow in this condition (Åkerlund & Andersson 1976; Åkerlund *et al.* 1976; Åkerlund *et al.* 1979; Strömberg *et al.* 1984). However, it remains to be shown whether changes in endogenous vasopressin release can affect the uterine activity and symptoms of dysmenorrhoea.

Combined oral contraceptives reduce menstrual pain (Milsom & Andersch 1984). This seems to be due to reduced spontaneous uterine activity and inhibition of the effects of the uterine stimulants arginine vasopressin and prostaglandin (PG) F$_{2\alpha}$ (Ekström *et al.* 1989). However, it is not known whether hormonal treatment with an oral contraceptive has an impact on the arginine vasopressin response to known stimuli of hormone release or on any resultant changes in uterine activity.

Therefore, we studied the vasopressin response to osmotic stimulation and the effects on uterine contractility during dysmenorrhoea and after one cycle of oral contraceptive treatment. Apart from vasopressin, we monitored the plasma concentrations of a PGF$_{2\alpha}$ metabolite during the experimental sessions, and also of oxytocin in view of the recent demonstration of both vasopressin and oxytocin receptors in the human non-pregnant uterus (Åkerlund & Andersson 1976; Maggi *et al.* 1990).

## Subjects and methods

Ten healthy nulliparous women, aged 20–28 years and with a history of moderate to severe primary dysmenorrhoea participated in the study. The women were recruited consecutively

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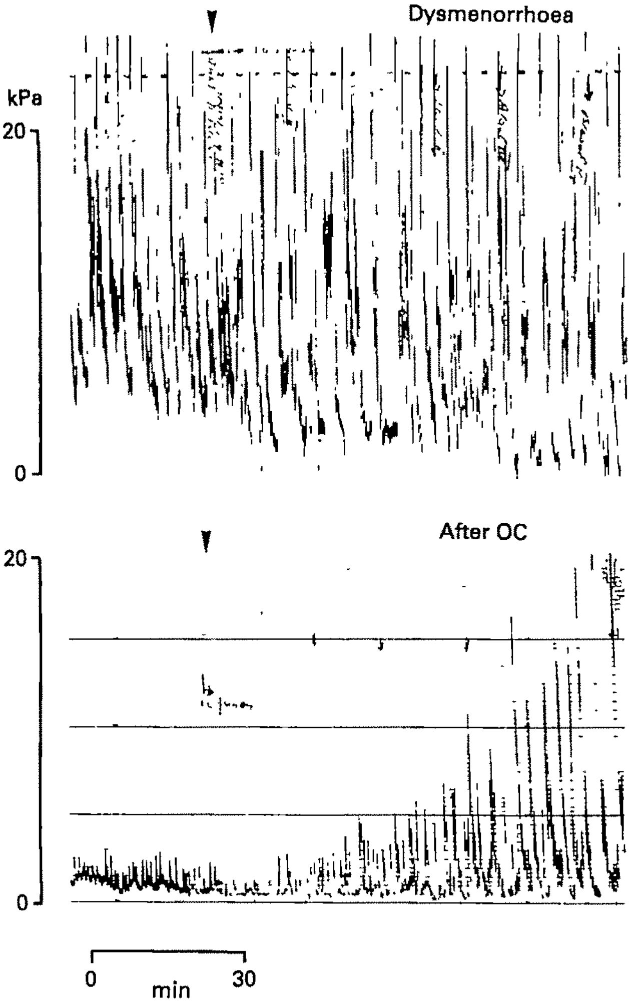

Fig. 1. Intrauterine pressure recordings in a woman on the first day of menstruation with intense dysmenorrhoeic pain (upper panel) and of the withdrawal bleeding after three weeks of oral contraceptive (OC) treatment (lower panel). At the arrows infusion of hypertonic salines was started

from women attending the out-patient department of the clinic and who agreed to participate. One of the women did not attend the second experimental session. They had not taken any oral contraception pills for at least 3 months before the study, had regular menstrual periods and none of them used an intra-uterine contraceptive device. The study was approved by the local ethics committee and the participants gave their written consent.

On the first day of a painful menstruation, the intrauterine pressure was recorded by using a microtransducer catheter (Model PC 350, Millar Instruments Houston, Texas; Åkerlund *et al.* 1978). After recording the spontaneous activity for 30 min, a continuous intravenous infusion of hypertonic saline solution (5% NaCl, 0·06 ml/kg/min; Baylis & Gill 1984) was given for 75 min. Plasma samples for the estimation of osmolality, arginine vasopressin, oxytocin and the PGF-metabolite, 15-keto-13,14-dihydro-$PGF_{2\alpha}$, were taken immediately before and at every 15 min during the infusion. Pulse rate and blood pressure were recorded at each sampling time. At the withdrawal bleeding after 3 weeks of oral contraceptive treatment with a daily dose of 30 µg ethinyl oestradiol and 150 µg levonorgestrel (Neovletta, Schering Nordiska AB, Stockholm, Sweden) the experimental procedure was repeated.

The blood samples for hormonal analyses were taken in chilled heparinized tubes, immediately separated and the plasma was stored at −20°C. Arginine vasopressin and oxytocin were analysed as described by Forsling (1985) and 15-keto-13,14-dihydro-$PGF_{2\alpha}$ was estimated according to Granström & Kindahl (1982). The intrauterine pressure recordings were quantified by planimetric analyses of the area under the recording curve over 10-min periods, i.e., the total pressure area (TPA).

Statistical comparisons of the results of plasma hormone estimations and uterine activity calculations were performed

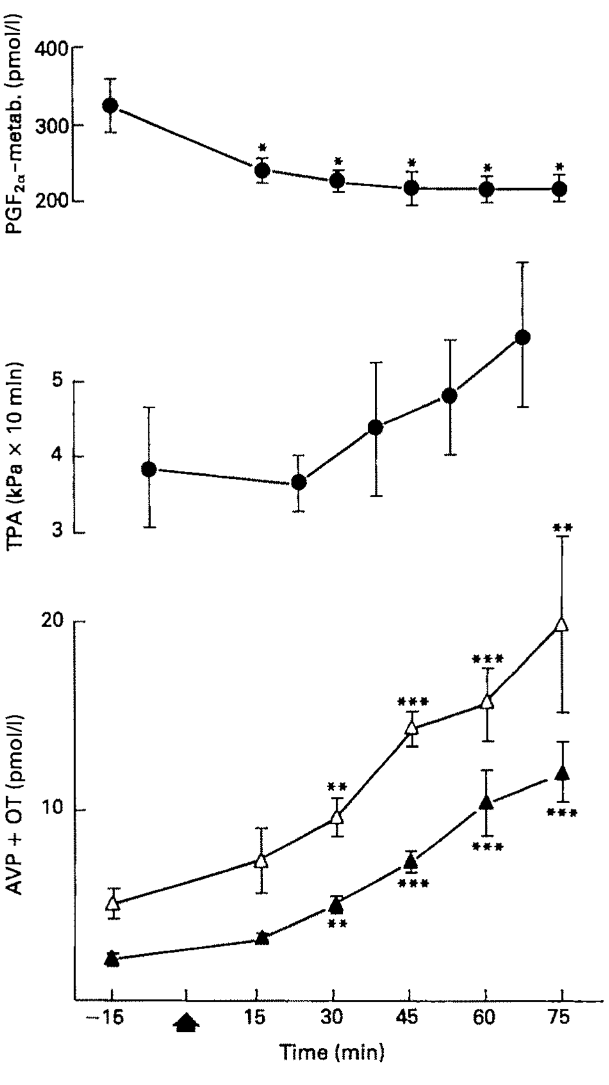

Fig. 2. Effect of hypertonic saline infusion (started at the arrow) on uterine activity, measured as total pressure area (TPA) ● —— ●, middle panel, and on plasma levels of arginine vasopressin (AVP) ▲ —— ▲, oxytocin (OT) △ —— △ and the $PGF_{2\alpha}$ metabolite 15-keto-13,14-dihydro-$PGF_{2\alpha}$ ● —— ●, upper panel, on the first day of bleeding in ten women with primary dysmenorrhoea. Means and standard errors are shown and statistically significant differences in comparison to the observations before start of infusion are indicated by asterisks (* = $P<0·05$, ** = $P<0·01$).

**Table 1.** Plasma concentrations of arginine vasopressin (AVP), oxytocin (OT) and 15-keto-13,14-dihydro-$PGF_{2\alpha}$ (PGF-metab and intrauterine pressure on the first day of menstruation in women with dysmenorrhoeic pain and at the withdrawal bleeding after 3 weeks of oral contraceptive (OC) treatment. Results before and after 75 min of infusion of hypertonic saline are compared

| | Dysmenorrhoea | After OC treatment | Significance of difference (*p*) |
|---|---|---|---|
| Arginine vasopressin | | | |
| Before infusion | 2·2 (0·3) | 0·9 (0·2) | <0·001 |
| After infusion | 12·0 (1·6) | 4·6 (0·6) | <0·001 |
| Oxytocin | | | |
| Before infusion | 5·0 (0·7) | 3·9 (0·6) | >0·05 |
| After infusion | 19·8 (4·6) | 16·4 (4·0) | >0·05 |
| Prostaglandin metabolite | | | |
| Before infusion | 321·0 (34) | 281·0 (31) | >0·05 |
| After infusion | 213·0 (16) | 181·0 (17) | >0·05 |
| Total pressure area | | | |
| Before infusion | 3·8 (0·8) | 1·3 (0·2) | <0·001 |
| After infusion | 5·5 (3·0) | 2·4 (0·4) | <0·01 |

by means of Wilcoxon's rank sum test for paired data, since the obtained results were found to be grossly normally distributed.

## Results

At the first recording session the women had moderate to severe dysmenorrhoea. The spontaneous uterine activity was generally intense with contractions of high amplitude and frequency, and an elevated uterine tone (Fig. 1, upper panel). After 3 weeks of oral contraceptive treatment, the women experienced minimal pain and the uterine activity was decreased (Fig. 1, lower panel).

The plasma concentrations of arginine vasopressin, oxytocin and the PGF-metabolite, as well as the total pressure area before and after 75 min of saline infusion in dysmenorrhoea and after oral contraceptive treatment is shown in Table 1. At both these times as well as in all other samples (not shown) significant decreases after oral contraceptive treatment were seen for vasopressin and TPA, whereas lowerings of plasma levels and oxytocin and the PGF-metabolite were nonsignificant (Table 1).

The mean osmolality initially was 296·0 (7·2) mosmol/kg and after the infusion 303·0 (6·2) mosmol/kg. After oral contraceptive treatment the corresponding results were 287·3 (5·2) and 295·0 (9·3) mosmol/kg, respectively. The effects of the infusion on plasma levels of hormones and on uterine activity before and after oral contraceptive treatment are shown in figures 2 and 3. On both occasions vasopressin and oxytocin increased significantly, while the PGF-metabolite showed a significant decrease. Pulse rate and blood pressure did not change.

During dysmenorrhoea, at the first recording period, the saline infusion stimulated the already high uterine activity (Figs. 1 and 2) and the pain was intensified. At the second session during painless withdrawal bleeding, the hypertonic infusion induced a significant rise in intrauterine pressure (Figs. 1 and 3) and the women also reported some menstrual pain.

## Discussion

The present results confirm the observed increased secretion of vasopressin and the $PGF_{2\alpha}$ in association with the uterine hyperactivity and pain of dysmenorrhoea (Åkerlund *et al.* 1976; Åkerlund *et al.* 1979; Strömberg *et al.* 1984), both of which were reduced by oral contraceptive treatment (Ekström *et al.* 1989). The inhibiting effect of the oral contraceptive on the uterine hyperactivity associated with dysmenorrhoea could be due to a decrease in vasopressin secretion and also to a lowered endometrial production of $PGF_{2\alpha}$. It is known that oestrogens can stimulate release of vasopressin and that this effect is counteracted by progestogens (Forsling *et al.* 1982). The oral contraceptives, particularly those in which progestogen predominates, as in the present study, might reduce the release of arginine vasopressin by changing the balance in ovarian hormones (Hauksson *et al.* 1987). Treatment with oral contraceptives also results in unsuccessful corpus formation and the rise in progesterone which is required for increased endometrial PG synthesis (Pickles 1967) is not seen.

At the first recording session, stimulation of endogenous vasopressin release by the hypertonic saline solution intensified the pain and tended to increase the already high myometrial activity. After one period of oral contraceptive treatment, when the spontaneous activity was comparatively low, the infusion induced a significant rise in intrauterine pressure and the women also reported more pain. These results suggests that factors increasing vasopressin release, may also stimulate uterine contractility and increase the pain of dysmenorrhoea. Factors inhibiting AVP-release, such as water overload might therefore have a therapeutic effect in the condition. This is in agreement with the early observation of Cobo *et al.* (1978).

In earlier reports (Hauksson *et al.* 1987; Ekström *et al.* 1989), we have discussed the possibility that oral contraceptives decrease the uterine sensitivity to vasopressin as a mechanism for their therapeutic effect. Present studies were not consistent with this theory, since stimulation of endogenous vasopressin release after one cycle of oral contraceptive treatment still caused pain and a significant increase in uterine activity. The discrepancy might possibly be explained by the fact that the increase in the plasma concentrations caused by injection of a lysine vasopressin in the previous studies was comparatively high, and above that of arginine vasopressin occurring during dysmenorrhoea, while the endogenously pro-

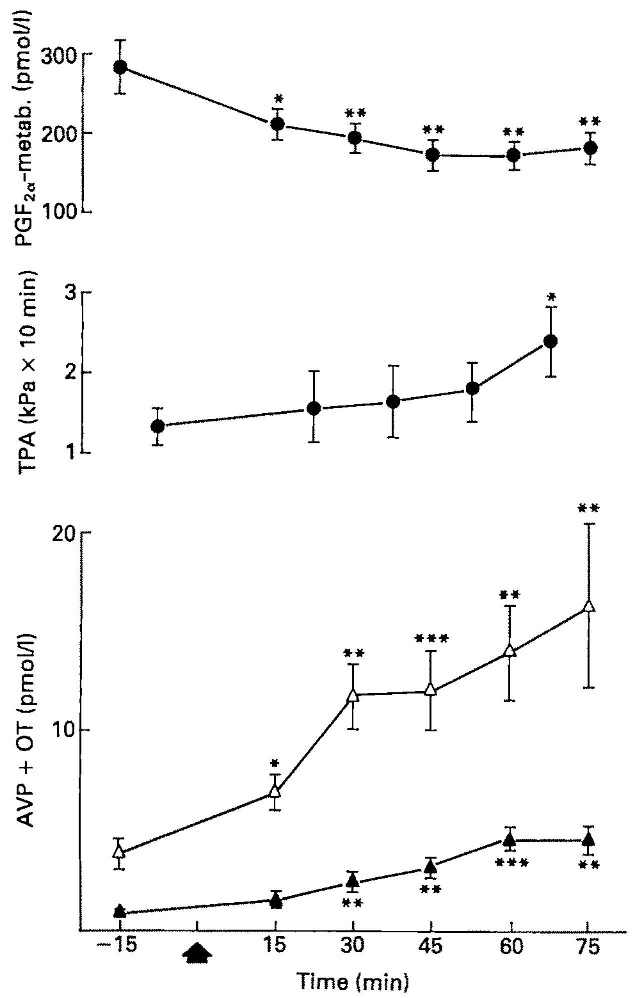

**Fig. 3.** Effect of hypertonic saline infusion (started at the arrow) on uterine activity measured total pressure area (TPA) ● —— ●, middle panel, and on plasma levels of arginine vasopressin (AVP) ▲ —— ▲, oxytocin (OT) △ —— △ and the PGF$_{2\alpha}$-metabolite 15-keto-13,14-dihydro-PGF$_{2\alpha}$ ● —— ●, upper panel, on the first day of bleeding in nine women regularly suffering from primary dysmenorrhoea, but now free of pain after one period of oral contraceptive treatment. Means and standard errors are shown and statistically significant differences in comparison to the observations before start of infusion are indicated by asterisks (* = $P<0{\cdot}05$, ** = $P<0{\cdot}01$). At the arrow infusion of hypertonic saline was started.

duced increase in the present study was more comparable with that occurring in pathophysiological conditions. Arginine and lysine vasopressin are about equipotent in their effects of the human uterus, but only the lysine analogue, which does not exist in the human but for example in the pig, is registered in Sweden for human use. Another explanation for the discrepancy with the earlier findings could be that those studies were done in women with no menstrual disturbances in whom stimulus of vasopressin is different from that in dysmenorrhoea.

The level of the PGF$_{2\alpha}$ metabolite decreased during the osmotic stimulation of vasopressin release, something which might be explained by initial increase in the production of prostaglandin due to stimulation of endometrial production by the intrauterine catheter. This reduction in PGF$_{2\alpha}$ release is not consistent with the results of an earlier pharmacological study with infusion of lysine vasopressin to healthy volunteers (Strömberg *et al.* 1984), where an increase in the PGF-metabolite was observed. The explanation for this inconsistency might again be differences in vasopressin concentrations. This suggests that vasopressin-induced stimulation of PGF-synthesis is of minor importance as a mechanism of dysmenorrhoea.

The present study demonstrated for the first time to our knowledge that infusion of hypertonic saline in dysmenorrhoeic women can cause an increase in oxytocin as well as vasopressin level. There is evidence that oxytocin is only a weak stimulator of the nonpregnant uterus (Coutinho & Lopes 1968), but this was obtained in studies using posterior pituitary hormone preparations of comparatively low purity. Our results together with the findings of separate oxytocin receptors also in the nonpregnant human uterus (Maggi *et al.* 1990) indicate the need for further studies on the role of oxytocin in the regulation of contractility of the nonpregnant uterus.

## Acknowledgments

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FETAL AND NEONATAL MEDICINE

# A four-year follow-up of hearing and development in children exposed *in utero* to vibro-acoustic stimulation

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**ABSTRACT**

**Objective** To obtain information of hearing and neuro-development in children exposed to vibro-acoustic stimulation *in utero*

**Design** Information collected from Swedish child care programmes.

**Setting** Department of Obstetrics and Gynaecology, Karolinska Institutet, Danderyd University Hospital, Sweden.

**Subjects** Children of 460 mothers exposed to vibro-acoustic stimulation for the assessment of fetal well-being during high- and low-risk pregnancies during 1985–1987.

**Main outcome measures** Auditory test (20–25 dB at eight frequencies between 500 and 8000 Hz) and general neurological examination at four years of age.

**Results** No hearing damage or neuro-developmental abnormalities that could be connected to the vibro-acoustic stimulation were found.

**Conclusions** Vibro-acoustic stimulation, as applied in clinical practice, did not endanger either neurological developement or hearing in children exposed *in utero*.

Since the fetal acoustic stimulation (FAS) test was introduced into clinical practice, a number of investigators have expressed concern about the possibility of harm to the fetus. Fetal reaction to the FAS test resembles the startle response of the newborn child (van Vliet *et al.* 1985). The stimulation results in a prolonged change in fetal behavioural state (Visser *et al.* 1989; Devoe *et al.* 1989; Gagnon *et al.* 1989), and it has been suggested that such changes might affect the neurodevelopmental integrity of the fetus. Caution has therefore been recommended (Gerhardt *et al.* 1988; Patrick 1989; Visser *et al.* 1989). Moreover, in more recent studies the sound pressure level *in utero* at vibro-acoustic stimulation has been shown to be high (Gerhardt *et al.* 1988; Nyman *et al.* 1991). As the FAS test has been widely adopted in clinical practice, we felt the long-term effects of vibro-acoustic stimulation should be investigated.

## Subjects and methods

A total of 525 children exposed to vibro-acoustic stimulation *in utero* were traced for the study. The vibro-acoustic stimulation had been performed in 507 pregnancies (420 high-risk pregnancies and 87 low-risk singleton pregnancies). Details of the main part of this series have been published previously (Westgren *et al.* 1987; Nyman & Westgren 1989).

Of the 438 children from 420 high-risk pregnancies, 41 could not be traced at their registered addresses, and six had died in the interim: four perinatally, one of the sudden infant death syndrome at 3 months of age, and one of meningitis at 2 years of age. Attempts were also made to trace the 41 missing children in the files at the Department of Audiology of Karolinska Hospital, where all children with hearing defects living in the Stockholm area are registered. The mothers of the missing children represented an average sample of the group; there were no particular diagnostic or social differences between them and the other mothers in this group.

The vibro-acoustic stimulation was administered to elicit fetal movements with a view to studying maternal perception of fetal movements as a measure of fetal well-being. The test procedure used was as follows: with the pregnant woman resting in a semi-recumbent position, the FAS test was administered by means of a Servox artificial larynx (Siemens, Cologne, Germany) placed close to the fetal head; vibro-acoustic stimulation was given for 1–3 s, and if the woman failed to perceive any fetal movements the test was repeated twice and the results were recorded. A mean of four FAS tests were performed per pregnancy (range 1–27), and their outcome and distribution by gestational age (between 28 and 43 weeks) are shown in Table 1.

The Servox artificial larynx produces a sound pressure level in air of 99 dB at a distance of 2 cm, though when the sound pressure level is measured *in utero* with a hydrophone, higher values are obtained—129 dB having been the maximum recorded by us (Nyman *et al.* 1991). The Servox device gives rise to a pattern of frequencies in the 30–10 000 Hz range, with a peak at 500 Hz.

The possibility of any injurious effects of the FAS test was investigated at the extensive 4-year-old check-up that forms part of the routine Swedish child care programme (see Table 2) in which all the remaining 478 children participated. This check-up includes an extensive interview with the accom-

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**Table 1.** Outcome of fetal acoustic stimulation (FAS) tests during different periods of pregnancy. Figures denote numbers of tests performed

| Outcome of FAS test | Gestation (weeks) 28–31 | 32–35 | 36–39 | 40–43 | Total |
|---|---|---|---|---|---|
| No. with fetal movements | 149 | 463 | 807 | 220 | 1639 |
| No. without fetal movements | 20 | 37 | 83 | 21 | 161 |
| Total no. | 169 | 500 | 890 | 241 | 1800 |

panying parent(s), a general physical examination of the child, checks of development, and tests of sight and hearing. The developmental check-up includes test of motor function (running, walking on toes/heels, balancing on a tilt-board, squatting, hopping on one foot, threading beads on a string, etc.), and a check of drawing ability and simple counting.

The auditory test is performed as follows: after first familiarizing the child with the equipment, including the headphone and objects he/she can move to indicate perception of the signal relayed by the head-phones; both ears are tested at 20–25 dB and at different frequencies in the 250–8000 Hz range (250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz). The signal is given twice at each frequency at random intervals. If the child fails to perceive the signal, usually due to infection (chronic otitis media), the test is repeated within a few weeks. If the child still fails to perceive the signal, he/she is referred to an ENT department.

## Results

Of the 478 children, 450 had normal hearing and development. Thirteen children repeatedly refused to undergo the audiological test, though they were all normally developed without any speech defect, and all had had normal distraction test results (Snashall 1988) at 9 months of age. These children had no particular characteristics with regard to social class or diagnosis during pregnancy.

**Table 2.** Basic child care monitoring programme run by the Swedish health services

| Age | Examiner | Content |
|---|---|---|
| 1 week | Nurse | Home visit 1–3 days after discharge from the maternity ward, information on accident prevention. |
| 2, 3 + 5 weeks | Nurse | Development and weight check. |
| 6–8 weeks | Doctor, nurse | Development check. |
| 3 months | Nurse | Development check, vaccination. |
| 4 months | Nurse | Development and weight check. |
| 5 months | Nurse | Development check, vaccination. |
| 6 months | Doctor, nurse | Development check. |
| 8 months | Nurse | Development check. |
| 9 months | Nurse | Hearing test (distraction test). |
| 10 months | Nurse | Development check. |
| 12 months | Doctor, nurse | Vaccination. |
| 15 months | Nurse | Information on accident prevention. |
| 18 months | Doctor, nurse | Vaccination, development check. |
| 2, 5 years | Nurse | Speech test, information on accident prevention. |
| 4 years | Doctor, nurse | Checks of development, sight and hearing. |
| 5, 5–6 years | Doctor, nurse | Vaccination, development check. information on accident prevention |

Six children had chronic otitis media at the first testing; one of them still has impaired hearing, while the other five are normal.

One child had impaired hearing in his right ear (3000–8000 Hz, 55–60 dB). He had been exposed to five vibro-acoustic stimulations *in utero*, resulting in maternal perception of fetal movements, at 36–41 weeks gestation. His mother had a similar hearing defect, which suggests the possibility of a hereditary hearing disorder.

Eight children were found to have some degree of handicap (Table 3), but none that could be related to the FAS test. One of the handicapped children (case no. 1, Table 3) was traced in the files of the Department of Audiology at Karolinska Hospital (see methods).

The outcome of all the tests is summarized in Table 4.

## Discussion

The present study comprised 478 children who had been exposed to vibro-acoustic stimulation *in utero* when the FAS test had been used in high- and low-risk pregnancies to investigate maternal perception of fetal movements as an indicator of fetal well-being. We were unable to detect any children with hearing disorders that could be related to the FAS test. Although the bulk of the original series consisted of high-risk pregnancies which, *per se*, increases the risk of fetal compromise, the frequency of development defects at 4 years of age was not higher than could be expected.

Gerhardt *et al.* (1988) have shown that the intrauterine sound pressure level in pregnant ewes exposed to vibro-acoustic stimulation to be rather high (134 dB), in agreement with our recent findings in women in early labour (Nyman *et al.* 1991). The duration of the FAS test in clinical application is usually limited to 3–5 s (sometimes repeated twice). If the sound pressure level is high, there might be a risk of damage to the organ of Corti resulting in impaired hearing. According to Lenoir *et al.* (1986), the critical period for acoustic trauma would appear to be when the cochlea has just acquired its adult functional properties. In humans this occurs between 24 and 28 weeks gestation (Johansson *et al.* 1964). Exposure to a very loud noise during that period might induce rupture of the basilar membrane of the cochlea and subsequent hearing loss (Bohne & Clark 1982). However, most of the FAS tests in our studies were performed after 28 weeks gestation.

As the fetal external and middle ear is surrounded by fluid, even if the fetus is exposed to a high sound pressure level, oscillation in the oval and round windows will be considerably less than that associated with comparable exposure in air. This protective effect of fluid may explain why in this series we found no children with severe hearing loss that could be attributed to the FAS test. Longer exposure might be more harmful, even if the attenuation of sound pressure levels in fluid can be estimated to be approximately 35 dB (Oliver 1989). Molvaer *et al.* (1981) have shown that long exposure to noise produced by a pneumatic rock drill under water can be hazardous to a diver's hearing. Although this might be worth bearing in mind,

**Table 3.** Handicapped children exposed to vibro-acoustic stimulation *in utero*

| Patient number | Obstetrical history | Fetal movements at FAST | Gestational age (weeks) |  | Mode of delivery | Apgar score | Handicap |
|---|---|---|---|---|---|---|---|
|  |  |  | At FAST | At birth |  |  |  |
| 1 | SGA, insemination 10 years infertility | 4/5 | 30–35 | 35 | LCS | 9, 10 | Corpus callosum agenesia, severe mental retardation, impaired hearing. |
| 2 | Fetal arrythmia | 3/7 | 36–37 | 38 | Normal vaginal | 9, 10 | Mental retardation—hearing test not possible. |
| 3 | Maternal pre-eclampsia | 4/6 | 29–41 | 41 | Normal vaginal | 7, 9, 10 | Mental retardation, normal hearing. |
| 4 | SGA | 1/1 | 40 | 40 | LCS | 8, 9 | Slight hemiparesis, normal hearing, normal development. |
| 5 | SGA | 4/5 | 34–38 | 38 | LCS | 9, 10 | Slight paresis—one leg, normal hearing. |
| 6 | Maternal hepatosis | 1/1 | 41 | 41 | Normal vaginal | 9, 10 | Down's syndrome. |
| 7 | Twins (second twin) | 3/3 | 38 | 39 | Ventouse (asphyxia) | 3, 7, 9 | Cerebral palsy with ataxia and atetosis, normal hearing, normal mental development. |
| 8 | Maternal abdominal trauma | 3/3 | 38 | 40 | Normal vaginal | 9, 10 | Autistic. |

FAST = fetal acoustic stimulation test, SGA small for gestational age LCS = low caesarean section.

such conditions are not properly comparable to those obtaining within the uterus, since divers have air surrounding the middle ear structures.

Douek *et al.* (1976) found circumstantial evidence of hearing damage in preterm babies exposed to the noise of an incubator. They showed that in newborn guinea pigs exposed to the same noise, there was destruction of a proportion of the sensory cells in the cochlea. Children who have required intensive care in incubators neonatally are known to manifest a hearing loss of 2–5% (Snashall 1988) but, at this stage, the baby's ear is not protected by fluid. Hearing damage may also be related to immaturity *per se*, as well as to intrauterine infection.

Since the prevalence of hearing loss in non-risk subjects is low (1:2000, Downs & Sterrit 1967), a much larger series than ours would be required to determine whether the FAS test is associated with an increased incidence of hearing disorders. The prevalence of impaired hearing is probably higher in a high-risk series than in a normal series although it is not possible to estimate exact figures.

It has been suggested that the FAS test might constitute a clinically useful means of fetal neurological examination (Divon *et al.* 1985). In the present study, children with subsequent handicap did not react in any particular pattern at the FAS test (Table 3). As used in these studies the FAS test does not permit children with mental or neurological disorders to be distinguished in the fetal state.

**Table 4.** Hearing and development in the children at 4 years of age

| Variable | No. of children | (%) |
|---|---|---|
| Normal development |  |  |
| Normal hearing | 455 | (95) |
| Hearing test not conducted | 13 | (3) |
| Chronic otitis media | 1 | (–) |
| Impaired hearing | 1 | (–) |
| Development disorders (Table 3) | 8 | (2) |
|  | 478 | (100) |

Ohel *et al.* (1987) studied auditory nerve and brainstem evoked responses 1–2 days after normal delivery in 40 babies who had been exposed to vibro-acoustic stimulation three times during early labour. No differences were found in auditory acuity between the exposed and control infants.

Arulkumaran *et al.* (1991) reported a follow-up study of four-year-old children who had been exposed to vibro-acoustic stimulation *in utero*, and whose hearing was tested at 1000 and at 4000 Hz. Since the peak value of the Servox device is 500 Hz (range 30–10 000 Hz), the present procedure including testing at lower frequencies seems to be a more suitable means of detecting possible hearing impairment. In view of the concern felt about possible risks associated with changes of fetal behavioural states, and as the FAS test can induce such changes, it is also important to search for potential neurological damage.

Although vibro-acoustic stimulation produces high intrauterine sound pressure levels, the fluid surrounding the fetal external and middle ear would seem to have a protective effect. To exclude the possibility that the FAS test has long-term effects on the fetus, a very large series would be needed. However, in this study there was no evidence of neurodevelopmental disorders or hearing damage in the children exposed to vibro-acoustic stimulation *in utero*.

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## CASE REPORTS

# Atypical female intersex

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## Case report

The patient described in this report was an adult married woman who first attended the Ramakrishna Mission Seva Pratishthan Hospital, Calcutta, India on 25 March, 1988.

She was 23 years of age and had been married for 5 years. Micturition and menstruation occurred through the anus, as did sexual intercourse. Urine also dribbled occasionally through a phallic urethra. She was continent of faeces. She was a phenotypic female with well-developed secondary sex characters.

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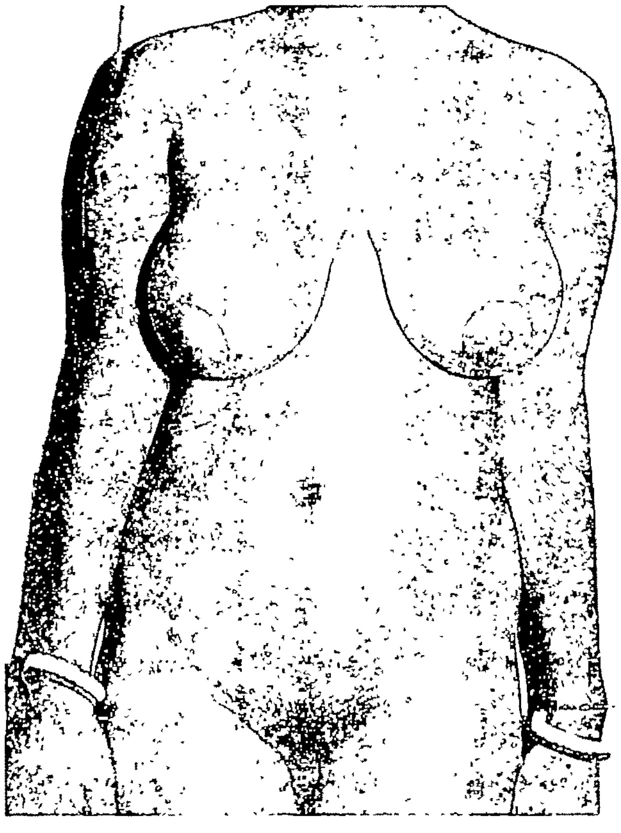

**Fig. 1.** 46 XX, phenotype female; well developed secondary sex characters and a large phallus.

The labia majora were normal but the pudendal cleft was obliterated, the perineal body absent and there were marked clitoromegaly with a meatal opening; part of the labia minora projected into the anorectal wall with concomitant shifting of the urethra and vagina into the rectum. The phallus was more anterior and more cephalad than normal and lacked the caudal curvature usual in women (Figs. 1 & 2). Compression of the distended shaft of the phallus caused small quantities of urine to spurt out.

There was no history of in utero exposure to androgenic agents. The haematological and endocrine investigations and excretory pyelogram were normal. A buccal smear was chromatin positive and repeated karyotypes were 46 XX. Ultrasonography and laparoscopy showed that she had a bicornuate uterus and tubal blockage at the fimbrial ends. Examination under anaesthesia, sigmoidoscopy and vaginoscopy revealed the vagina and, caudal to it the urethra, opening into the

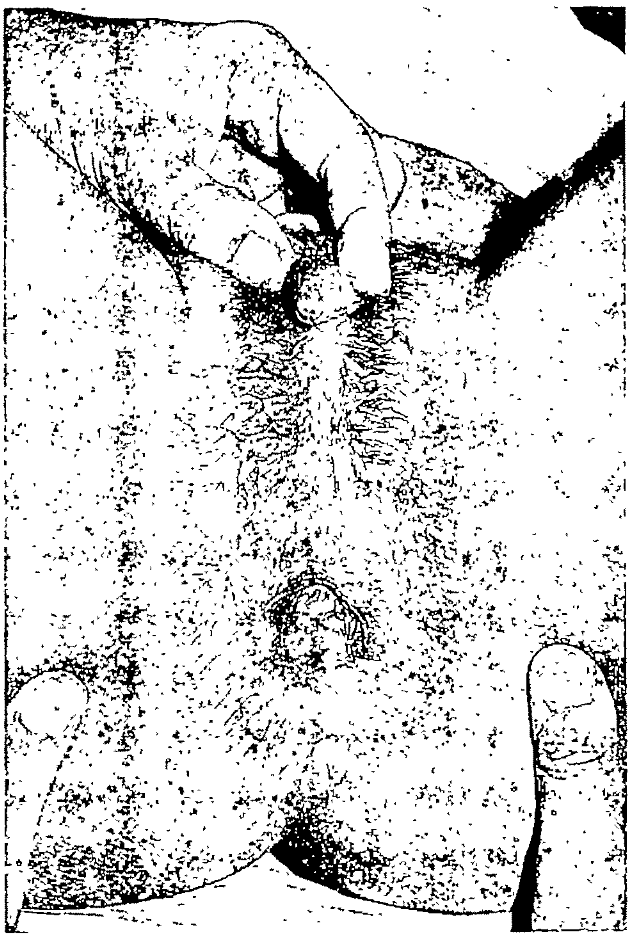

**Fig 2.** External genitalia with well developed labia majora, fused pudendal cleft, retro-placed labial vestibule encroaching the anal canal, and the large phallus with meatal opening on the glans.

anterior rectal wall about 5 cm cephalic to the anus; the cervix and sagittal septum in the upper third of the vagina could be palpated through the anus (Fig. 3). A fine polythene tube was introduced with difficulty through the phallic meatus and a cystoscope through the rectal urethra. Cystoscopy showed normal ureteric orifices and two separate urethral openings; retrograde catheterization detected no anomalies. Contrast injected through the phallus and rectal urethra on separate occasions confirmed phallic megalourethra with outlet obstruction.

At abdomino-perineal reconstructive surgery on 24 June, 1988, the bicornuate abnormality of the uterus was confirmed and there were bilateral peritubal adhesions with fimbrial occlusion; biopsies of the gonads showed normal ovarian histology. The vagina, which was adherent to the anterior rectal wall, was separated around the rectovaginal communication. The dissection was extended in the para-rectal space down to the pelvic floor and the puborectalis muscle and the anorectual ring were identified following the principle of Goligher's operation (Goligher 1958, 1975) for rectal prolapse (Fig. 4).

A perineal procedure followed: liberal para-anal incisions opened the para-rectal space; the pubococcygeus and the puborectalis muscles were identified. The vaginal and urethral openings were located through the stretched anal orifice, separated and dissected by incising the rectal mucosa around the upper (posterior) lip of the vagina.

The urethra, vagina and the associated vestibule, and labia minora were displaced enmasse forwards and downwards and anchored in near to the normal position by opening the pudendal cleft. The rectal mucosa was repaired longitudinally and the anus reconstituted with tightening of the sphincters. The puborectalis muscles were sutured together in front of the rectum, and the pubococcygeus and laterally displaced perineal muscles were used to construct the perineal body (Fig. 5). The phallus was excised and the accessory urethra ablated (Figs. 6, 7). The post-operative recovery was uneventful. She achieved normal menstruation and micturition through the re-directed genitourinary passages.

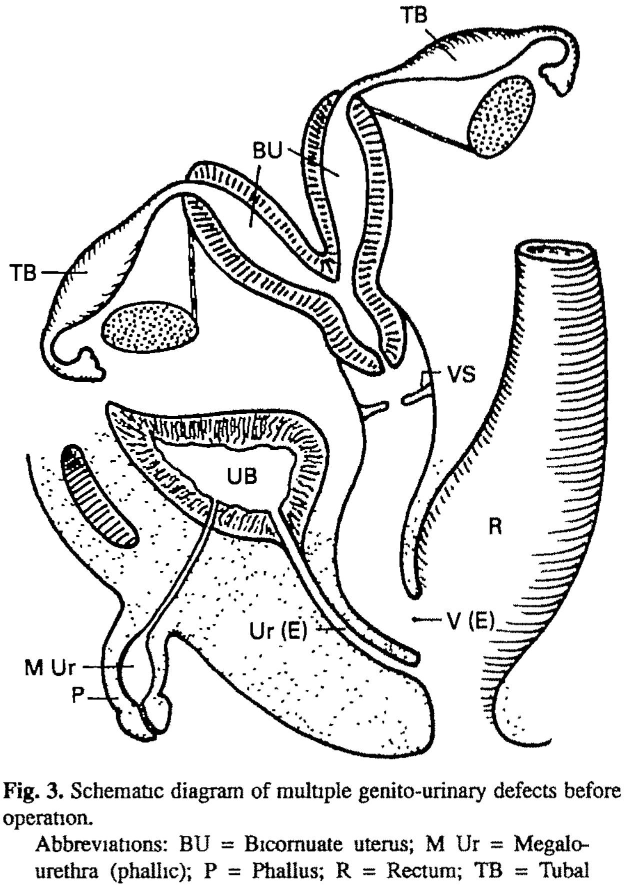

**Fig. 3.** Schematic diagram of multiple genito-urinary defects before operation.

Abbreviations: BU = Bicornuate uterus; M Ur = Megalourethra (phallic); P = Phallus; R = Rectum; TB = Tubal blockage (bilateral); Ur (E) = Ectopic urethra; UB = Urinary bladder, VS = Vaginal septum.

A hysteroplasty and bilateral tuboplasty were performed at the second laparotomy on 17 September, 1988. She conceived 15 months after the last operation and remained in hospital throughout her gestation. A healthy female baby (birthweight 2·5 kg) was born by elective caesarean section on 25 July, 1990.

The genital organs, ovaries and the bladder were assessed again during the casarean section; a weak area in the ventral wall of the bladder where the phallic urethra opened was incised and repaired. A 4 cm urethral length was confirmed later by a micturating cystogram and cystourethrogram (Fig. 8). The excised phallus measured 5×2 cm and had a median skin raphe on the caudal surface; the glans was well developed and had a meatal opening; cross-sections showed a single fibro-elastic cylinder traversed by the megalourethra.

## Discussion

Idiopathic female intersex (Park *et al* 1972) involving a spectrum of urogenital anomaly, with or without cloacal malformation, is rare (Johnson *et al* 1972; Klugo *et al.* 1974; Kounami *et al.* 1986; Turnock & Rickwood 1987). Most are diagnosed at birth or during infancy. Park *et al.* (1972), further to the observations of Blum (1904), classified female intersex into five groups: (i) Congenital adrenal hyperplasia; (ii) maternal androgenic influence, either exogenous or endogenous; (iii) idiopathic masculinization without somatic anomalies; (iv) special group with serious somatic anomalies and (v) familial group.

The present patient is unusual and belongs to group (iii). A

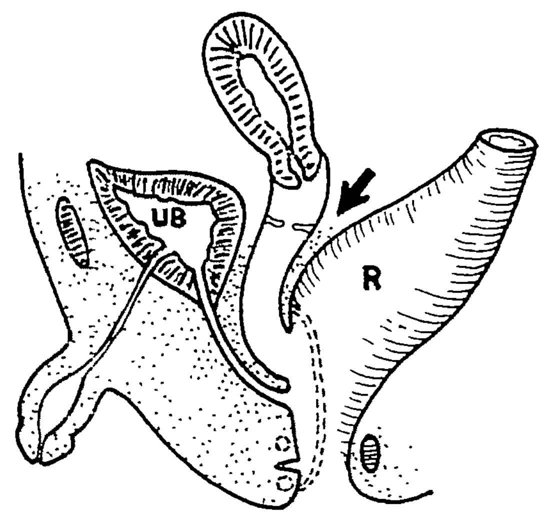

**Fig. 4.** Planning of abdomino-perineal operation. UB = Urinary bladder; R = Rectovaginal septum.

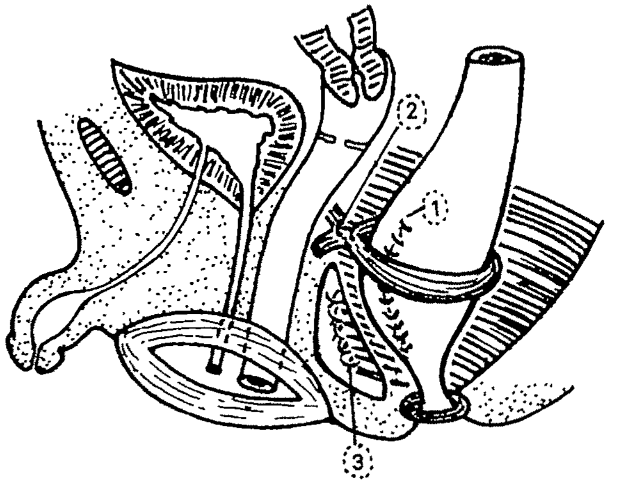

**Fig. 5.** Schematic presentation of reconstructive surgery before excision of phallus. (1) Repair of anterior rectal wall at the site of ectopic opening of vagina and urethra; (2) Anterior approximation of puborectalis muscle; (3) Reconstruction of perineal body.

few similar cases have been reported by Grubenmann (1912), Howard & Hinman (1951), Bonney *et al.* (1975) and Thiry *et al.* (1979); the last two groups of authors claimed theirs to be the 4th and 5th instance in literature but Bellinger & Duckett (1982) and Kounami *et al.* (1986) recently analysed 19 cases including their own. The clinical features varied widely. The ectopic openings of the vagina and urethra inside the rectum, with accessory phallic urethra as in our patient, have not been described before. This has been confirmed by many through personal communication (The Royal Society of Medicine, UK; Royal College of Obstetricians & Gynaecologists, UK; Prof S. S. Ratnam, Singapore; Prof John E. Skandalakis, Georgia, USA; Sir John Stallworthy, UK; Prof Peter L. Williams, UK; Prof Carl Wood, Australia).

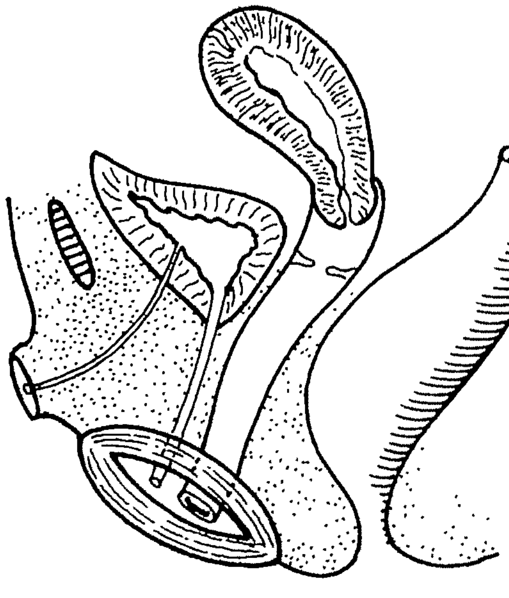

**Fig. 6.** Correction of external genital malformations with ablation of phallic urethra and excision of the phallus

The simple idiopathic group comprises a range of urogenital anomalies and degrees of phallic differentiation (Kounami *et al.* 1986). A functional double urethra has been recorded in a few cases (Grubenmann 1912; Jones & Scott 1971; Bonney *et al* 1975; Belis & Hrabovsky 1979; Hurwitz & Fitzpatrick 1982), but 'Y'-type duplication is more frequent (Perloff *et al* 1953; Jones & Scott 1971; Bellinger & Duckett 1982). The phallic urethra was stenotic in most cases with a terminal stricture (Hurwitz & Fitzpatrick 1982). The rectal urethra functioned normally in our patient so that there was no obstructive uropathy.

In the normal woman, the ventral corpus spongiosum does not differentiate, resulting in an absence of a phallic urethra and causing a ventral curvature. The clitoral prominence in the present case may be accounted for by phallic urethralization, as suggested by Bellinger & Duckett (1982), which prevents the development of a normal female ventral chordee. The terminal stricture of the phallic urethra, as observed by many (Bonney *et al.* 1975; Belis & Hrabovsky 1979; Hurwitz & Fitzpatrick 1982), is the result of separate development of this part from an ectodermal groove on the undersurface of the corona glandis (Bellinger & Duckett 1982; Marberger 1975). The megalourethra is the result of abnormal development of the phallus, but there is controversy about the fibro-elastic cylinders (Belis & Hrabovsky 1979; Huben *et al.* 1981; Kounami *et al.* 1986). Surgical treatment of the phallic urethra is not often

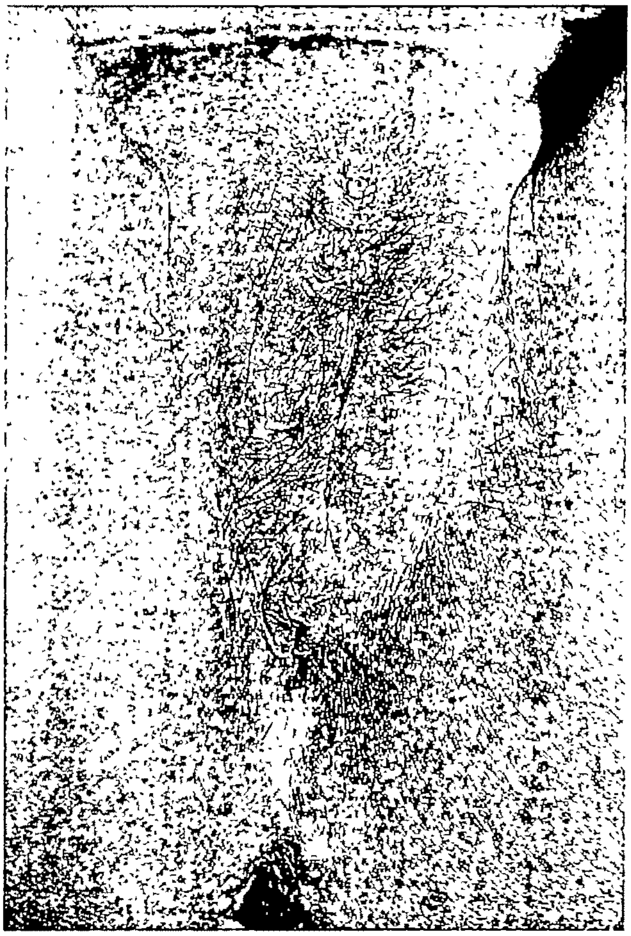

**Fig. 7.** A close view of the external genitalia, after reconstructive surgery.

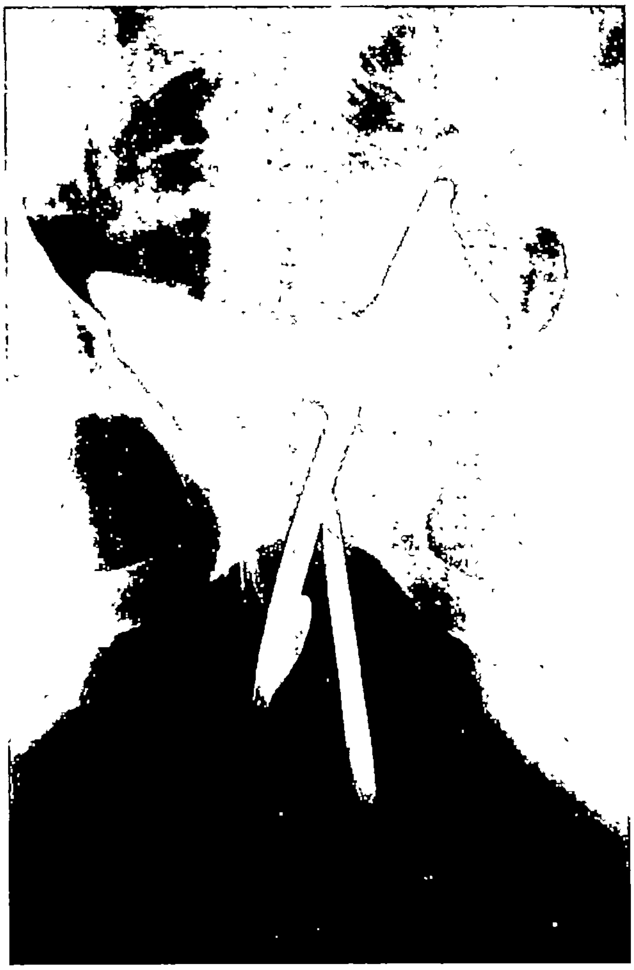

Fig. 8. Post-operative cysto-urethrogram showing the 4 cm length of the urethra relocated from the rectum.

necessary as little urine usually passes through it (Bellinger & Duckett 1982).

Diagnosis is usually at birth or in early childhood because of the ambiguous external genitalia, but there may also be obstructive uropathy, urinary tract infection and frequent dribbling of urine. Supra-pubic cystostomy and cutaneous nephrostomy have been necessary when there was severe urinary tract obstruction (Grubenmann 1912; Belis & Hrabovsky 1979). The treatment is usually directed towards relieving urinary obstruction and correcting the masculinized external genitalia. Clitoridectomy has now been replaced by clitoroplasty relocating normal caudal curvature to reduce the phallic prominence and to preserve normal clitoral sensation. The excess shaft skin has been used to reconstruct the labia minora (Bellinger & Duckett 1982). The internal genitalia rarely require surgical correction, but reduction vaginoplasty and vaginal septotomy (Hurwitz & Fitzpatrick 1982) are recorded.

Laparotomy is not necessary for the assessment of gender (Bellinger & Duckett 1982). Uteroplasty and tuboplasty were essential in the present patient as such a major degree of uterine deformity might have not been compatible with term pregnancy. Clitoridectomy was obligatory as clitoroplasty was technically difficult because of the high anatomical location of the phallus.

The embryological pathogenesis in the present case is difficult to ascertain. Possibilities include a local disturbance of the inductive factor (Howard & Hinman, 1951), resulting from an incomplete union between the Müllerian ducts and the urogenital sinus; this might be responsible for the uninhibited development of an accessory phallic urethra.

The urethralization of the female phallus is distinguishable from masculinization in adreno-genital syndrome by the presence of both phallic and vulval urethral orifices. Turnock & Rickwood (1987) suggested that this may be due to failure of differentiation of the peri-cloacal mesoderm, because of late arrival and incomplete fusion of the Müllerian ducts.

Our patient had unique multiple atypical genito-urinary deformities and surgical correction was followed by a successful pregnancy. Such a case has not been described before.

## Acknowledgments

The author is grateful to staff, Department of Obstetrics & Gynaecology, R.K.M.S.P. Hospital for their assistance; to Dr Asim Kr Dutta, Professor of Anatomy, University College of Medicine, Calcutta for his guidance; the secretarial staff for their support and the Secretary of the hospital for kind permission to use the hospital data. He is thankful to the numerous scientists for personal communication and especially to the Librarians of the Royal College of Obstetricians & Gynaecologists and the Royal Society of Medicine, UK, for computer search and reprints.

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# Intermittent abdominal decompression: an option for prevention of intrauterine growth retardation

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## Case reports

### *Patient 1*

A 26-year-old healthy woman was admitted in the 12th week of her sixth pregnancy because of her bad obstetric history. All her previous pregnancies had been complicated by hypertension and severe intrauterine growth retardation; the first three pregnancies were terminated between 26 and 32 weeks gestation because of intrauterine fetal death accompanied by moderate to severe hypertension. In her fourth pregnancy caesarean section was performed at 31 weeks gestation because of moderate hypertension, a small fetus, oligohydramnios and a positive oxytocin challenge test. The infant, who weighed 700 g at birth, died 4 days later from cardiorespiratory failure. The fifth pregnancy was terminated at 28 weeks gestation, again because of moderate hypertension and the death in-utero of a very small fetus. She was treated in this pregnancy by bed rest, hydralazine, methyldopa, low dose aspirin and prednisolone. No underlying cause was found for the recurrent hypertension, poor fetal growth and intrauterine death. On admission in her sixth pregnancy her blood pressure was 130/85 mmHg. She was treated with intermittent abdominal decompression using a Heyns' suit (Heyns 1963) with negative pressure of around 70 mmHg for 30 s every minute for 30 min twice a day. In addition she was treated by methyldopa. Her blood pressure during the pregnancy did not exceed 120/85 mmHg. Fetal growth was monitored by repeated ultrasonographic examinations and was normal. Repeated systolic/diastolic (S/D) ratios were calculated from the umbilical artery flow velocity waveforms obtained by continuous Doppler ultrasound, values ranged between 3·3 and 3·7. Umbilical artery flow velocity waveforms were not recorded during treatment with decompression because the ultrasound transducer could not be used within the sealed unit. At 38 weeks gestation a healthy 3280 g male infant was born by caesarean section.

### *Patient 2*

A 27-year-old healthy woman was admitted in the 15th week of her fourth pregnancy because of her bad obstetric history. She developed moderate hypertension during her first pregnancy which ended in intrauterine fetal death at 28 weeks. In her second pregnancy labour was induced at 37 weeks because of moderate hypertension and a small fetus. A 1900 g infant was born vaginally. No underlying cause for the recurrent hypertension was found. In her third pregnancy she was treated by bed rest, low dose aspirin (100 mg/day) and dipyridamole (225 mg/day). At 32 weeks gestation intrauterine death occurred. In her fourth pregnancy treatment with intermittent abdominal decompression, as described for patient 1, was initiated at 15 weeks. Her blood pressure was normal throughout the pregnancy and no drug treatment was given. Repeated S/D ratios, calculated during the treatment period from umbilical artery flow velocity waveforms, were below 3·5. At 39 weeks gestation a normal 4100 g male was born spontaneously. In her fifth pregnancy she used the decompression suit at home

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and was not admitted to hospital and again the pregnancy was normal with the birth of a normal healthy 3600 g infant.

### *Patient 3*

A 36-year-old hypertensive woman was admitted in the 12th week of her fourth pregnancy because of recurrent pregnancy aggravated hypertension. She had taken antihypertensive drugs for the previous four years. Her blood pressure under this treatment was 130–145/90–105 mmHg. Her three previous pregnancies were complicated by hypertension and her last two babies had been very small. In her second pregnancy she gave birth spontaneously to a 1800 g infant in the 37th week. In her third pregnancy she was treated, in addition to the antihypertensive drugs, by bed rest, low dose aspirin and dipyridamole. She was delivered spontaneously in her 37th week of a 1600 g infant. On admission in her fourth pregnancy her blood pressure was 140/90 mmHg under treatment with propranolol (10 mg twice daily). Intermittent abdominal decompression was begun as described for the other two patients. Under this treatment her blood pressure declined gradually to normal levels and, from 25 weeks gestation, the antihypertensive treatment was discontinued. Repeated S/D ratios from the umbilical artery were found to be between 2·2 and 1·8 even in late pregnancy. Her creatinine clearance which was 100 ml/min in the first trimester was 182 ml/min at 37 weeks. At 39 weeks gestation a 2700 g healthy and normal male was born spontaneously. Five weeks after delivery her blood pressure rose again to 160/105 mmHg without antihypertensive treatment.

All three patients had normal values for the following investigations: kidney function, glucose tolerance, tests for autoimmune diseases including anticardiolipin antibodies, blood clotting functions and serology for toxoplasma, ureoplasma and chlamydia.

## Discussion

Reduced placental perfusion is probably a factor in the pathophysiology of recurrent intrauterine growth retardation development in many cases (Nylund *et al.* 1983; Berkowitz *et al.* 1988; Cunningham *et al.* 1989). A variety of treatments have been assessed during the last two decades. Aspirin, corticosteroids, dipyridamole and heparin have been administered with partial success (Henk *et al.* 1987). About 30 years ago, Heyns (1963) described his experience with intermittent abdominal decompression in the last 12 weeks of pregnancy for reducing the occurrence of pre-eclampsia. He and others claimed that abdominal decompression during pregnancy resulted in improved maternal blood flow through the intervillous space (Coxon & Haggith 1971; Stange & Vaklavinkova 1983). This method was shown by Varma & Curzen (1973) to improve fetal growth and outcome in pregnancies with suspected intrauterine growth retardation. It has also been reported that this procedure results in a significant rise in urinary oestriol output suggesting better fetoplacental metabolism (MacRae *et al* 1978). The value of abdominal decompression in the treatment of pregnancy-induced hypertension is uncertain. Blecher & Heyns (1967) treated women with pre-eclampsia and found that maternal and neonatal morbidity was less than in the non-treated group. On the other hand, Coxon *et al.* (1973) found that routine antenatal decompression starting from 28 weeks gestation did not alter the frequency of pre-eclampsia nor the neonatal outcome in a high risk population. A commentary by Hofmeyr (1990) reviewed the published research and suggested that further studies into the beneficial effects of abdominal decompression were warranted.

The three patients we describe present a new approach to the use of an old technique which once aroused much interest but then failed to gain wide acceptance. Much evidence was gathered regarding the ability of intermittent abdominal decompression to increase blood flow in placental intervillous space (Heyns 1963; Coxon & Haggith 1971; Stange & Vaklavinkova 1983; Varma & Curzen 1973) yet, the clinical results were often unsatisfactory.

Campbell & Hackett (1986) were the first to demonstrate that in women with recurrent fetal growth retardation increased placental vascular resistance can be detected by measuring Doppler blood flow velocity waveforms in the umbilical and arcuate uterine arteries as early as the end of the first trimester or beginning of the second trimester of pregnancy. It is accepted that treatment intended to prevent the development of hypertensive disease of pregnancy and associated fetal growth retardation should be started at about 12-16 weeks gestation (Henk *et al.* 1987). The efficiency of such preventive treatment is very difficult to prove in individual pregnancies and requires randomized controlled trials on large series of patients. A cumbersome and time-consuming procedure such as abdominal decompression is very difficult to test on a large scale from a very early stage of pregnancy, and convincing confirmed statistical proof of its efficiency has not been obtained.

The three patients described appear to demonstrate a very dramatic benefit as a result of the decompression technique in women in whom the currently accepted methods of treatment had failed. The very early start of the treatment may explain the differences between the success of treatment in our patients and the uncertainty of the effect of this treatment in the past. We are aware that these cases do not provide any definite proof for the efficiency of this treatment but they strongly suggest that some women who experience recurrent fetal intrauterine growth retardation and who do not respond to the other available treatments may benefit from intermittent abdominal decompression started late in the first trimester.

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# The effect of thyroxine replacement on menstrual blood loss in a hypothyroid patient

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## Case report

A 46-year-old woman was referred to the gynaecology outpatient clinic with menorrhagia that had been getting worse for the previous year. No abnormalities were detected during general and pelvic examination. An admission for dilatation and curettage of the uterus was arranged. The resulting endometrial histology report read 'menstrual, early and late secretory endometrium, irregular ripening and shedding'.

She was subsequently seen in the outpatient department and given a brief and unsuccessful course of norethisterone. On review several months after stopping the norethisterone, in addition to continuing menorrhagia, she also complained of lethargy and a poor complexion. On physical examination she was slim, (51 kg and 1.63 m tall), pale, normotensive, had flaking dry skin and thinning dull hair. Serum thyroid function studies, a day 21 progesterone estimation and a full blood count were arranged. The patient agreed to collect her soiled sanitary material so that the volume of her menstrual blood loss could be measured. The alkaline haematin method was employed for this purpose (Hallberg & Nilsson 1964), and menorrhagia was defined as a menstrual blood loss of ≥80 ml. An initial menstrual collection (whilst taking no medication) showed a blood loss in that cycle of 479·7 ml. The thyroid function study results became available and were indicative of hypothyroidism—thyroid stimulating hormone (TSH) >60 IU/l and free thyroxine (free T4) 1.3 pmol/l. The normal ranges for a euthyroid woman are 0·5-2·5 IU/l for TSH and 2·0-8·0 pmol/l for free thyroxine. The progesterone result was consistent with anovulatory cycles. Her haemoglobin concentration was 11·1 g/dl.

She was seen shortly afterwards in the endocrinology clinic where the diagnosis was confirmed. Thyroxine replacement started at an initial dosage of 50 µg daily for 1 week, then increasing to 100 µg daily which was continued for 3 months, when the dosage was increased further to 150 µg. The patient continued to menstruate at approximately 4 week intervals and agreed to collect her soiled sanitary material, thus enabling monitoring of the menstrual blood volume (Fig. 1). Her menstrual loss after 5 days of thyroxine treatment was 201·9 ml. Two cycles later the loss was reduced to 58 ml, and was again within the normal range at 69 ml the following month. Thyroid function studies demonstrated clear improvement: after 5 weeks of treatment, TSH was 6·7 IU/l and free T4 was 5·3 pmol/l and after 4 months TSH was 1·1 IU/l and free T4 was 3·9 pmol/l (within the normal range).

In addition to the resolution of menorrhagia, the patient reported a dramatic improvement in her general well-being. Some 12 months later, however, she returned to the gynaecology clinic stating that her menses had once again become excessive and requesting a hysterectomy. Unfortunately, no further menstrual collections were made and the magnitude of this blood loss is not known. A total abdominal hysterectomy was subsequently performed and the uterus appeared normal when examined by the histopathologist.

## Discussion

Menorrhagia is the most common cause of iron deficiency ana-

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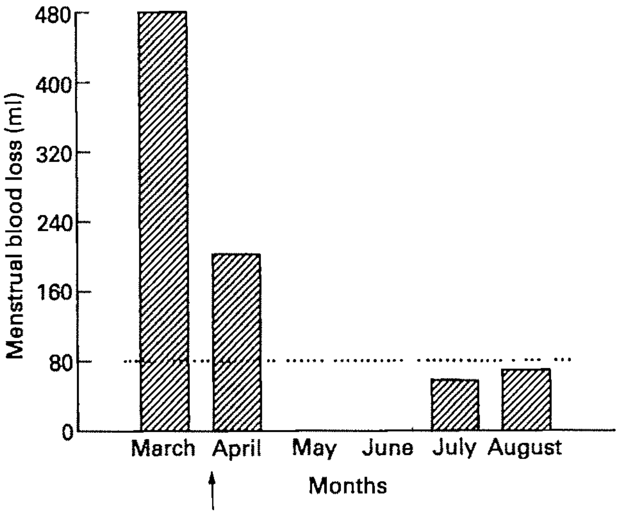

**Fig. 1.** Menstrual blood loss in a hypothyroid woman treated with thyroxine replacement. The arrow indicates the beginning of thyroxine therapy.

emia in the reproductive years (Cohen & Gibor 1980). Excessive uterine bleeding is associated with a variety of local and systemic pathology (Dockeray 1988). Hypothyroidism is frequently quoted in this context, although there are few objective data to support this assertion. In one study, in which 50 hypothyroid women were questioned, abnormal menstrual patterns were present in 56% (Scott & Mussey 1964). Amongst these, menorrhagia was the most common complaint. One woman had her menses measured and was found to be losing 135 ml. In another publication in 15 women with 'early' hypothyroidism, the subjective complaint of menorrhagia disappeared when corrective doses of thyroxine were given (Wilansky & Greisman 1989). Unfortunately, menstrual quantification was not performed on any of these patients.

This case report supports the concept of an association between hypothyroidism and menorrhagia. A study involving a much larger number of hypothyroid women remains long overdue.

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## SHORT COMMUNICATIONS

# Unexpected pathological findings in uterine prolapse: a 12-month audit

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After any gynaecological operation it is common practice for excised tissue to be sent for histological examination whatever the indication. In an increasingly cost conscious climate the need for every excised specimen to be studied histologically has been questioned (Brooks & Hughes, 1987; Alun-Jones *et al.* 1990). Conversely the rise in medical litigation and the need to confirm clinical diagnoses may halt this trend towards selective histopathology.

Vaginal hysterectomy and pelvic floor repair for uterine prolapse is an example of an operation where significant pathology is not anticipated in the excised specimen. However, many patients with prolapse are elderly and are therefore at risk of developing a gynaecological malignancy. Since most uterine carcinomas arise from the cervix or endometrium, it is from these areas that routine blocks are taken for microscopic examination (any macroscopically abnormal areas are also sampled). We have examined the surgical files of the Northern General Hospital, Sheffield, over a 12-month period to study the frequency of unexpected pathology in patients with uterine prolapse.

A total of 552 hysterectomy specimens were received by the laboratory during the 12-month study period (1/10/90–30/9/91), of which 371 were removed for a variety of benign conditions, 95 for malignancy and 86 for uterine prolapse. Table 1 shows the pathological lesions found in the specimens removed for prolapse. Incidental lesions, such as endometrial polyps or fibroids requiring no further treatment, were found in 45 of the 86 specimens. Significant lesions, defined as those which would require an alteration from the routine clinical management, were identified in two of the 86 specimens (2·3%). One of these was an endometrioid adenocarcinoma, Grade 3, arising in the endometrial cavity of a 55-year-old woman. The tumour was 2 cm in diameter and infiltrated more than half the depth of the myometrium. As a direct result of this unexpected finding, this patient has since received radiotherapy. The second was a well differentiated squamous cell carcinoma of the cervix from a 50-year-old woman, 1 cm in diameter and invading to a depth of 0·4 cm. It was clinically Stage 1b and therefore no further treatment was considered necessary but the patient will require prolonged follow-up.

## Discussion

During a 12-month period, carcinoma was identified unexpectedly in two of 86 hysterectomy specimens removed for uterine prolapse. The importance of these findings is that in both patients the clinical care was directly changed by the histological report.

The identification of these cases illustrates the importance of examining all surgical specimens histologically, whatever the indication for operation. In some branches of surgery, it has been suggested that it is unnecessary to submit all excised tissue for histological examination, perhaps because it is thought unlikely that any significant lesion will be present, if it cannot be identified macroscopically; for example, Brooks & Hughes (1987) suggested that macroscopically inflamed appendices did not need to be sent for histology. However, serosal inflammation does not necessarily imply transmural true appendicitis, but may be secondary to inflammation elsewhere in the abdomen, for example salpingitis (Channer & Jenkins 1988). A recent survey of ear, nose and throat surgeons revealed variable practices in respect to the examination of nasal polyps: 38% sent all excised polyps whilst the remainder sent only those which appeared abnormal. In support of this selective histopathology, they found that all tumours identified histologically had been suspected clinically. In contrast, in our study neither tumour was suspected clinically.

Another field where selective histopathology has been con-

**Table 1.** Histological lesions identified in 86 patients with uterine prolapse

| Type of lesion | *n* |
|---|---|
| Incidental lesions | |
| Leiomyomas (single or multiple) | 33 |
| Endometrial polyps | 13 |
| Adenomyosis | 12 |
| Endocervical polyps | 6 |
| Simple hyperplasia | 1 |
| Endometriosis | 1 |
| Human papilloma virus infection | 1 |
| Total | 67* |
| Significant lesions | |
| Endometrial carcinoma | 1 |
| Carcinoma of the cervix | 1 |
| Total | 2 |

*Multiple lesions present in some specimens.

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sidered is in minor surgery. A recent study showed that only a proportion of specimens were sent for examination: only 31% of specimens from a surgical day theatre (Hillan *et al.*, 1991). However, several reports have stressed the importance of submitting all specimens for histology, whatever the suspected diagnosis, due to the occasional unexpected identification of a malignant tumour, and for the assessment of the adequacy of excision (McWilliam *et al*, 1991; Whimster & Leonard, 1991).

From the results of our audit of hysterectomy specimens removed during pelvic floor repair, we would strongly support the practice of submitting all specimens for histology.

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# Sex ratio, testosterone and postpartum thyroid dysfunction

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The sex ratio (proportion of boys) of infants born to women with postpartum thyroid dysfunction is reportedly low. Table 1 gives all the data known to me on the topic. The pooled data yield a $\chi^2$ of 11·9 ($P<0\cdot001$) when tested against an expected live birth sex ratio of 0·514 (James 1987a). I offer an explanation of this phenomenon.

Postpartum thyroid dysfunction is associated with the HLA antigens A1 and B8 (Leader 1987). The latter antigen has been found to be associated ($P<0\cdot05$) with low testosterone levels in women (Gerenčer *et al.* 1982). These authors also reported that A1 (a rarer antigen) was associated with the lowest mean testosterone level of all the 12 antigens they tested in women. So assuming no linkage disequilibrium between these genes, the combination of A1 and B8 would be expected to be associated with low testosterone at beyond the 0·01 level. Since the links between the HLA genes and testosterone levels are thought to be causal, there is the strong suggestion that postpartum thyroid dysfunction is associated with low testosterone levels.

**Table 1.** Sexes of offspring of women with given diagnoses

| Source | Males | Females | Diagnosis |
|---|---|---|---|
| Amino *et al.* (1982) | 6 | 22 | Postpartum thyrotoxicosis and hypothyroidism |
| Farid *et al.* (1983) | 8 | 17 | Postpartum thyroiditis with transient thyrotoxicosis |
| Fung *et al.* (1988) | 21 | 28 | Postpartum thyroid dysfunction |
| | 35 | 67 | |

The measure of heterogeneity of these data is not significant ($\chi^2 = 3\cdot7$; $0\cdot2>P>0\cdot1$) and it seems valid to pool them.

I have adduced a substantial quantity of data to support the hypothesis that the hormone levels of parents at the time of conception are associated with the sexes of resulting offspring, low levels of testosterone being associated with subsequent female births (James 1987b). Accordingly, I suggest that the low sex ratio of infants born to women with postpartum thyroid dysfunction may be caused by their low testosterone levels at the time of conception.

The present hypothesis may readily be tested in two ways. (1) The hormone levels of these women should be assayed. If the hypothesis is correct, then unusual hormone levels are expected to characterize the women at all times (not just at the time of conception). In particular, I suggest that their testosterone levels are low. It is possible also that they have low oestrogen and/or high gonadotrophin levels. (2) The sexes of the other children born to these women should also be examined. If the hypothesis is correct, there will be an excess of females.

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## BLAIR BELL RESEARCH SOCIETY

# Papers presented at the meeting on 17 January 1992 at the London Hospital Medical College, Royal London Hospital, Whitechapel

**Effect of frequency of uterine contractions on human fetal cerebral oxyhaemoglobin concentration measured by near infrared spectroscopy (NIRS)** by D. M. Peebles, A. D. Edwards, J. S. Wyatt, A. P. Bishop, M. Cope, D. T. Delpy & E. O. R. Reynolds. Departments of Obstetrics, Paediatrics & Medical Physics and Bioengineering, UCMSM, Rayne Institute, London WC1E 6JJ.

Frequent uterine contractions may impair feto-maternal gas exchange in the placenta and cause fetal hypoxia. The purpose of this study was to employ the novel technique of NIRS to measure the effect of uterine contraction frequency on fetal cerebral oxyhaemoglobin concentration ($HbO_2$) during labour. Two specially designed optic fibres were placed at a fixed distance from one another via the cervix 3 or 4 cm apart on the fetal scalp after rupture of the membranes. Continuous data on changes in ($HbO_2$) were collected for 6 term fetuses for a median duration of 276 (range 45–765) mins. Five of these labours were augmented by an infusion of oxytocin. The timing of uterine contractions was measured by external tocography. In each fetus between 45 and 60 mins of continuous data where tocography clearly demonstrated uterine contractions were analysed. Changes in cerebral $HbO_2$ were calculated from the start of one contraction to that of the next and were related to the time interval between the two contractions (measured from peak to peak on tocography). Changes during 86 pairs of contractions were studied with a median of 14 per fetus (range 9–22) and the results are shown in the table below:

| Contraction interval (mins) | *n* | $\Delta HbO_2$ (μmol.100g$^{-1}$ mean ± SD |
|---|---|---|
| 0–1·49 | 20 | −0·36±0·26 |
| 1·50–2·99 | 40 | −0·06±0·35 |
| 3·00–4·49 | 20 | 0.46±0·28 |
| 4·50–5·99 | 6 | 0·77±0·37 |

The positive relation between $\Delta HbO_2$ and contraction interval was highly significant ($P<0{\cdot}001$, ANOVA) and the variation between individual fetuses was small. Short contraction intervals were consistently associated with a fall in $HbO_2$. The median contraction interval below which $\Delta HbO_2$ was negative has been calculated in each fetus and was 2·3 (range 1·4–2·4) minutes. We conclude that: (1) A significant relation was demonstrated between contraction interval and $\Delta HbO_2$. (2) For each fetus there was a critical contraction interval below which a net fall in cerebral $HbO_2$ was observed. If successive contractions occurred more frequently than this there was insufficient time for recovery of $HbO_2$ to baseline.

**A simple technique for the culture and subculture of human fallopian tube epithelial cells** by M. E. Kervancioglu, J. Martin, S. D. Maquiness, O. Djahanbakhch. London Hospital Medical College Academic Department of Obstetrics and Gynaecology, The Royal London Hospital, London E1 1BB.

Fallopian tubes from 11 women, aged 35-46 years, were removed at hysterectomy for uterine fibroids. The mucosal folds were cut into 1mm pieces and taken into a culture flask consisting of Earle's balanced salt solution supplemented with fetal bovine serum and antibiotics. After 7-10 days of primary culture, the explants were removed to separate the components of the culture flask; primary culture procedure was then repeated. After the explants were removed, the remaining adherent cells were trypsinized and passaged. New epithelial cells were seen after 3–4 days of primary culture and epithelial patches were observed after 7–10 days of primary culture. Only one culture was contaminated with fibroblasts and was discarded. In primary culture, ciliary activity was observed in some cells; however, this phenotype not observed in subcultures. In subculture, population doubling time was 4–5 days. The epithelial cells had a life span of 42–60 days. Immunofluorescence staining showed that more than 80% of the cells in the primary culture and subcultures were of epithelial origin. Similarly transmission electron microscopic examinations of these cells showed secretory characteristics of epithelial cells. We have demonstrated that fallopian epithelial cells can be cultured *in vitro*, using a simple technique and conventional culture media. Thus we may be able to expand our knowledge and understanding of fallopian epithelial cell function using this simple and long life technique.

**Six new cervical carcinoma cell lines and their use as a model for invasion and metastasis** by D. Eustace*, X. Han**, S. Money**, B. Dagg**, E. Heyderman**, Departments of Gynaecology* & Histopathology**, UMDS, St. Thomas Hospital, London SE1 7EH.

Six new cervical epithelial cell lines, XH1, EH2, DE3, EL4, JE6 and SM7 have been derived from six different squamous or adenosquamous cervical carcinomata and established in long term monolayer culture. All the cell lines grow as flat, adherent, polygonal cells. Karyotyping and DNA profiling has shown the cell lines to be distinct from each other. XH1, EH2, DE3 and JE6 have so far been investigated and found to form xenografts in nude mice which show invasion into muscle, nerves and blood vessels. XH1 produces lung colonization following intravenous injection. Two subpopulations of cells have been cloned from both XH1 (XH1a & XH1b) and EH1 (EH1a & EH1b). Within each pair the 'a' and 'b' populations differ morphologically as well as in their behaviour *in vivo*. The 'a' clone in each case is very similar to the parental cell line with adherent polygonal cells in culture, forming xenografts and causing lung colonization in the mouse. Each 'b' clone, however, has a slower rate of doubling in culture with a more diffuse pattern of growth. The cells are flat hemispherical or spindle-shaped. Subcutaneous injection of these cells into the mouse results in rapid cell growth from 1–2 weeks, but this is always followed by cystic degeneration, regression and disappearance. The epithelial origin of all these cells have been confirmed by the demonstration of tonofilaments and desmosomes on electron microscopy and by staining with epithelial markers. All the cell lines have HPV type 16 incorporated into their genome with copy numbers between. The raising of antibodies to the tumour cells may have applications in screening and treatment. Cytokine production by all the cell lines is currently being investigated. These cell lines provide a model of invasion, 'metastasis', and regression in human cervical carcinoma, which has potential for the study of the various cellular mechanisms that may be involved in these processes, including tumour suppressor genes (P53), metastasis suppressor genes (*nm*23), and growth factor secretion and receptor expression.

**Can failed fertilized human oocytes be used as an alternative to pre-implantation embryos in research?** by N. J. Winston*, J. K. Artley**, P. R. Braude**, D. M. Sutton** & M. H. Johnson*. *Department of Anatomy, University of Cambridge & **Assisted Conception Research Unit, UMDS Department of Obstetrics and Gynaecology, St Thomas Hospital, London SE1 7EH.

Research involving the use of pre-implantation human embryos raises many difficult ethical and moral problems. However, the extrapolation of data obtained from other mammalian embryos, such as the mouse, to the human may lead to erroneous conclusions being drawn. In some animal species, oocytes can be stimulated to divide in the absence of sperm and these parthenotes have been used to study aspects of embryogenesis in those species. We have now developed a system that will result in the activation of at least 60% of human oocytes by using the calcium ionophore A23187. Of the resulting parthenotes, 68% had only one pronucleus, 14% had two, and the remainder had either 3 pronuclei or showed immediate cleavage. Cleavage as far as eight-cell stage, but not beyond, has been observed. In addition to demonstrating that parthenotes are capable of cleavage, examination of their protein synthetic patterns has shown that some are capable of synthesizing proteins associated with morulae and blastocysts derived from fertilization *in vitro*. Thus some parthenotes are capable of normal gene expression and protein synthesis. Taken together these data suggest that activated oocytes might provide a suitable model for the investigation of the early mechanisms of development and cell division in the human, overcoming the ethical objections to the use for this purpose of pre-implantation embryos resulting from fertilisation *in vitro*.

**Cumulative pregnancy rates for in vitro fertilization — embryo transfer: 1982–1989** by R. de Courcy-Wheeler, Institute of Obstetrics and Gynaecology, Royal Postgraduate Medical School, DuCane Road, London W12 0HS.

All cycles of *in vitro* fertilization (IVF) initiated between 1982 and 1989 were analyzed retrospectively. They included those couples who dropped out before completing a cycle for any reason. The outcome was assessed by the pregnancy rate achieved per cycle from which the cumulative pregnancy rates (CPR) were calculated. Pregnancy was diagnosed by visualizing a gestation sac and pulsating fetal heart 28 days after embryo transfer, combined with rising titres of beta human chorionic gonadotropin hormone on days 14 and 28. Preclinical abortions were not included. 1569 couples underwent 2952 cycles of IVF. The mean pregnancy rate was 17·95% per cycle, 25·23% per egg collection and 32·39% per embryo transfer. The CPR per cycle initiated rose from 17·3% to 80·2% after 6 cycles. The CPR per egg collection increased from 24·9% to 69·3% after 4 cycles. There was no difference in the success rates between the total group and subgroups of tubal disease, unexplained infertility and maternal age of 36 and under. IVF is a successful treatment of infertility. To derive the maximum benefit, couples should be encouraged to persist for 4 treatment cycles which reach the egg collection stage in anticipation of a 70% pregnancy rate.

**Pretreatment of the uterine cervix in first trimester terminations of pregnancy** by J. C. Cooper, G. Robinson, M. P. Cust & G. M. Filshie. Queen's Medical Centre, University Hospital, Nottingham NG7 2UH.

Termination of pregnancy is a common procedure. Damage to the cervix may occur during serial dilatation and any procedure that decreases the force required should, therefore, decrease the long term complications such as mid-trimester abortion, due to cervical incompetence. We measured the force required to dilate the cervix in 120 first trimester terminations of pregnancy, comparing 3 different pretreatments. Laminaria (a hygroscopic dilator) and cervagem (gameprost) were compared with those patients who received no cervical pretreatment. The force required to serially dilate the cervix was measured using a Filshie Cervical Force Recorder. The mean force required for dilatation with each size dilator was calculated and the 3 groups compared. In nulliparous patients the force required to dilate up to and including a 10 mm dilator was significantly less in both treated groups when compared to the no pretreatment group. There was no difference between the two treatment groups themselves. In multiparous patients, the force required was similarly decreased up to and including a 9 mm diameter dilator; however, in this group the decrease was not statistically significant. In both groups, dilatation past an 11 mm diameter results in a decrease in force. This probably represents a disruption in cervical integrity. It appears that pre-treatment of the cervix with either laminaria or cervagem results in a decrease in force required to dilate the cervix and thus, it is hoped, a reduction in the long term morbidity of this common procedure.

**The use of first trimester amnifiltration in prenatal diagnosis of fetal karyotype to limit amniotic fluid removal** by D. L. Byrne, K. Marks, P. R. Braude & H. Nicholaides*. Department of Obstetrics and Gynaecology, St. Thomas Hospital, London SE1 7EH & *Harris Birthright Research Centre for Fetal Medicine, Kings College Hospital, London SE5.

Early amniocentesis is technically possible from 8 weeks gestation; however, successful culture of cells is not reliably achieved until after 10 weeks gestation. From this stage in pregnancy, amniotic fluid culture is as successful as conventional genetic amniocentesis, because the proportion of viable cells is greater in the first trimester. Whilst the safety of the procedure is unknown, the major concern of is that the relatively high proportion of amniotic fluid removed may result in impaired fetal pulmonary development and function, as has been suggested by animal studies. Our amnifiltration system fulfills the same function as early amniocentesis but with removal of only 1 ml of amniotic fluid. We have already established the best filter material and pore size, and it demonstrated that a minimum circulation volume of 20 mls is required to obtain a clinically useful result. In 38 pregnancies, prior to elective termination at 10–14 weeks gestation, amnifiltration was performed. A mean circulation volume of 29 mls (range 20–40; SD=6) was used, and a successful cell culture and normal karyotype was obtained in all cases. The mean number of clones generated in culture was 14 (range 4–30; SD=6) and mean harvest time of cultures was 11 days (range 7–14 days; SD=2). Subsequent to this pilot study amnifiltration has been successfully carried out in 20 ongoing pregnancies. After ultrasound guided insertion of a 20 gauge needle, 24 mls amniotic fluid was circulated across a 0·8 µm pore size cellulose acetate filter, in three passes. The procedure was uncomplicated in all cases. This is the first ever report of amnifiltration in the first trimester, harvest and culture times will be presented along with pregnancy outcome to date.

**Endothelium dependent relaxation in diabetes in pregnancy** by A. L. McCarthy, C. Lowy, P. Taylor, K. S. Raju & L. Poston. Departments of Gynaecology, Physiology and Unit of Endocrinology & Diabetes, UMDS Smooth Muscle Group, St Thomas' Campus, London SE1 7EH.

Abnormal endothelial function has been implicated in diabetic vascular disease, and impaired endothelium dependent relaxation has been demonstrated in the resistance vasculature in animal models of diabetes. Gestational diabetes (GDM) is complicated by an increased incidence of pre-eclampsia, though the underlying reason for this is not understood. We sought to examine endothelium dependent relaxation of resistance arteries in pregnancies complicated by gestational diabetes in the absence of hypertension. Resistance arteries of control (CTR) normotensive pregnant women ($n$ = 12, mean diameter = 266 ± 17·6µ SEM) and of those with gestational diabetes ($n$ = 7, mean diameter = 248 ± 22·04) were dissected from subcutaneous fat biopsies obtained at the time of caesarian section and mounted on a small vessel myograph. Acetylocholine (ACh) mediated relaxation was studied ($10^{-9}$M—$10^{-5}$M) in arteries pre-contracted with 3µM noradrenaline. ACh induced relaxation was markedly attenuated in arteries of women with gestational diabetes and maximal relaxation was impaired ($5\times10^{-6}$M. 97·14% ± 3·2 in CTR versus 71·46% ± 28·42 in GDM; $P<0{\cdot}01$). These results suggest that relaxation of the resistance vasculature is impaired in GDM. This may be relevant to the increased incidence of pre-clampsia in diabetic pregnancy.

**Reflex cardiovascular responses to acute hypoxia in term fetal sheep** by D A. Giussani, J. A. D. Spencer, P. J. Moore, L. Bennet & M. A. Hanson. Department of Obstetrics and Gynaecology, UCL, London WC1E 6HX.

In term fetal sheep, episodes of acute isocapnoeic hypoxia produce an increase in femoral vascular resistance, abolished by cutting the carotid sinus nerves and by treatment with phentolamine (PA). To investigate the complexity of the efferent pathways of this reflex, we studied the effect of (1) carotid chemodenervation and α-adrenergic blockade and (2) administering exogenous arginine-vasopressin (AVP) into chemodenervated fetuses treated with PA, on this response. Twenty-four fetal sheep (119–126 days gestation) were chronically instrumented under general anaesthesia (1g thiopentone for induction; 2–3% halothane in $O_2$ for maintenance). Catheters were placed in a carotid artery, a jugular vein and the amniotic cavity. Flow probes (Transonic, Ithaca, New York) were implanted around the other carotid artery and a femoral artery. In ten fetuses the carotid sinus nerves were identified and cut bilaterally. On the fourth post-operative day acute fetal isocapnic hypoxia was induced for 1h by reducing maternal $F_iO_2$. The following day, after giving either PA (Rogitine, Ciba; bolus dose 17–23mg followed by an infusion of 0·2mg/min) to intact and chemodenervated fetuses, or the same PA treatment coupled with a physiological infusion of AVP (Pitressin, Parke Davis; 5 mU/min) into chemodenervated fetuses, the protocol was repeated. Whilst all chemodenervated fetuses ($n$=10) treated with PA died during hypoxia, 9/14 intact fetuses treated with the α-antagonist survived. Moreover, 5/7 denervated fetuses treated with both PA and AVP also survived the hypoxic challenge. We conclude that survival of chemodenervated fetuses in hypoxia is impaired by PA due to blockage of catecholamines released from the adrenal gland. Since most of the intact fetuses treated with PA survived the hypoxic challenge, the role of other mechanisms mediated via the carotid chemoreceptors which are not α-adrenergic must be considered. Our data suggests that the release of AVP during hypoxia may be such a mechanism and that it may contribute to fetal survival during acute hypoxic challenges.

**New fetal antigens** by K. Price, R. Silman & J. G. Grudzinskas. Academic Unit of Obstetrics and Gynaecology, London Hospital Medical College, London E1 1BB.

Two fetal antigens, fetal antigen 1 (FA-1) and fetal antigen 2 (FA-2), were first identified in second trimester amniotic fluid by Fay *et al.*, as reported in the *European Journal of Obstetrics and Gynaecology,* Volume 29, 1988. Earlier immunohistochemical localization studies have suggested an endodermal origin for FA-1 (present in fetal liver and fetal pancreas), whereas FA-2 appears to be associated with mesodermal tissues (present in fetal skin and bone). This study was undertaken to generate the reagents necessary to further characterize the nature and occurrence of FA-2. Characterization of FA-2 using chromatographic techniques has revealed the presence of several forms of FA-2 in amniotic fluid. A five-step purification schedule has been developed for one of these forms, and the purified material has been used to generate polyclonal antibodies. Both the purified protein and the generated antibody have been shown to be suitable as reagents for setting up a sensitive radioimmunoassay.

**The comparison of models for the determination of iron absorption in healthy women** by J. F. R. Barrett, P. G. Whittaker, J. G. Williams* & T. Lind. Department of Obstetrics and Gynaecology, University of Newcastle & *NERC, ICP-MS Facility, University of London.

Stable isotope methods are currently used to investigate the extent of the increase in absorption of dietary iron during pregnancy. In order to be certain that this new methodology is accurate, the results obtained using stable isotopes and Inductively Coupled Plasma Mass Spectrometry (ICP-MS) were compared with those obtained using radioisotopes and whole body counting. 5mg of stable isotope 54-Fe was administered to 5 healthy non-pregnant women who had been eating a diet consisting of an average iron content (13mg/day) for three days The 54-Fe served as a carrier for 185 kBq of radio-isotope Fe59 (0·5mSv). An ampoule of the isotope, 57-Fe, was then given intravenously. From serum samples taken over the next 10h, the ratios of the stable iron isotopes were measured using ICP-MS and the oral iron absorption calculated. This was then compared to the result obtained by measuring the gamma activity emitted by the radioisotope using a whole body counter. The measured iron absorption ranged from 10%–45% The two methods showed good agreement across the entire range of the measurements, varying by not more than 5%. In conclusion, as new methodologies arise, it is essential that these are assessed before the results obtained are accepted. This study validates the use of stable isotopes and post absorption serum curves as a new and accurate technique in the measurement of iron absorption.

**Falloposcopy (transcervical tubal endoscopy) — a clinically useful tool?** A. Lower, O. Djahanbakhch & G. Grudzinskas. Joint Academic Unit of Obstetrics, Gynaecology & Reproductive Physiology, The London Hospital Medical College, Whitechapel, London E1 1BB.

The development of a new fibre-optic endoscope with an outside diameter of 0·5mm and a sophisticated linear eversion catheter delivery system has allowed transcervical cannulation of the fallopian tubes to be reliably achieved. We have obtained images of the fallopian tube from the uterotubal junction to the fimbriae. A short video demonstrating some of the findings and introducing the catheter delivery system is presented. This technique is currently under prospective comparative evaluation at this centre. We report on the strategy for evaluation for diagnostic use and discuss the potential therapeutic benefits which include assessment prior to tubal surgery, investigation and treatment of proximal tubal obstruction, embryo and gamete transfer to the fallopian tube under direct vision, treatment of ectopic pregnancy including the local administration of drugs (eg. methotrexate) and embryoscopy. These procedures can all be performed on an outpatient basis without the need for general anaesthetic, surgical incision or pneumoperitoneum.

**Evidence for the *in vitro de novo* synthesis of immunoglobulin and previously undescribed 17 kDa protein (TEP-2) by the mucosa of the fallopian tube** by K. Shrimanker, S. D. Maguiness, O. Djahanbakhch & J. G. Grudzinskas. Academic Unit of Obstetrics and Gynaecology, The London Hospital Medical College, The Royal London Hospital Trust, Whitechapel, London E1 1BB, and Newham General Hospital, Glen Road, Plaistow, London E13 8RU.

*De novo* synthesis and secretion of proteins by short-term explants of matched fallopian tube mucosa and endometrium were studied using radiolabelled L-($^{35}$S) methionine and $^{3}$H-glucosamine. To directly compare each anatomical site of the fallopian tube and endometrium from the same source, newly synthesized proteins were separated on one-dimensional polyacrylamide gel electrophoresis and examined by autoradiography. *De novo* synthesis of two protein bands provisionally designated as tubal epithelial protein 1 (TEP-1) and tubal epithelial protein 2 (TEP-2), was observed in explants of the fallopian tube mucosa obtained from each anatomical site throughout the ovarian cycle ($n = 20$). TEP-2 was not apparent in tubal mucosa obtained from postmenopausal women ($n = 5$). *De novo* synthesis of TEP-1 and TEP-2 was not apparent in autoradiographs of radio-labelled proteins from short-term explants of endometrium. From the autoradiographs, the molecular mass of TEP-1 and TEP-2 was calculated to be 25 kDa and 17 kDa respectively. TEP-1 was observed to be immunochemically similar to immunoglobulin $\kappa$ light chains. Antibodies generated against the 17 kDa protein band reveal different specificities in the fallopian tube and the endometrium.

**Pregnancy associated plasma protein-A, a first trimester screening test for chromosomal anomalies** by M. Macintosh*, I. Bonacchi**, B. Brambati**, T. Chard*, J. G. Grudzinskas*, A. Lunzani**, S. McGuinness*, K. Shrimanker*, B. Teisner*** & L. Tului*. *Joint Academic Unit of Obstetrics, Gynaecology and Reproductive Physiology, St Bartholomew's Hospital Medical College and the London Hospital Medical College; **Institute of Obstetrics and Gynaecology, University of Milan, Milan, Italy; & ***Department of Medical Microbiology, Odense University Hospital, Odense, Denmark.

The relationship of first trimester maternal serum pregnancy associated plasma protein-A (PAPP-A) with chromosomal anomalies was determined and its value as a screening test applied to the general population quantified. The median maternal serum PAPP-A in 30 viable pregnancies with abnormal chromosomes was 0·29 multiples of the median (MoM) compared with 0·94 MoM in 439 unaffected viable pregnancies. Offering karyotyping to women aged 37 and over (5% of maternities) will detect 22% of chromosomal anomalies whereas using an upper cut-off value for maternal serum PAPP-A of 0·295 MoM will detect 51% of chromosomal anomalies at the time of chorionic villus sampling for a 5% false positive rate. Combining the age and serum PAPP-A level will increase the detection rate to 56%. Provided there is no bias in selecting abnormal pregnancies destined to miscarry, biochemical screening using maternal serum PAPP-A has the potential of at least doubling the current detection rate of chromosome anomalies and offering the opportunity of antenatal diagnosis within the first trimester.

**Hormone replacement therapy with estraderm and norethisterone acetate patches** by J. Q. Norman–Taylor, F. Crawford & J. G. Grudzinskas. Department of Obstetrics and Gynaecology, The Royal London Hospital, London E1.

Eighteen postmenopausal women who had not had previous hormone replacement therapy were recruited to this study. Pretreatment investigations included an endometrial biopsy with hormonal and biochemical profiles. Treatment consisted of continuous application of Estraderm 50 and a norethisterone acetate patch on days 17 to 28. Fifteen women completed at least 6 months of treatment, with one woman withdrawing because of an allergic reaction. Good cycle control was established in 13 patients. Endometrial biopsy taken at 6 months showed secretory activity in 56% of cases. Norethisterone assay demonstrated a small intra-individual variation and a wide inter-individual variation (range 300pmol/l–1700pmol/l). Mean values for each cycle demonstrated consistent levels with no increase after multiple dosing (variation 5%). There was no relationship between the plasma levels of norethisterone and the tendency to have a withdrawal bleed. We have been able to demonstrate the viability of using the transdermal route as a mode of delivery of norethisterone for use in hormone replacement therapy.

**Is luteal function maintained by factors other than human chorionic gonadotrophin in early pregnancy?** A. Lower, J. Yovich*, C. Hancock* & G. Grudzinskas. Joint Academic Unit of Obstetrics, Gynaecology and Reproductive Physiology, The London Hospital Medical College, London E1, UK & *PIVET Medical Centre, Perth, Western Australia.

Fourteen women with ectopic pregnancy and nine women with early embryonic arrest ('blighted ovum') were studied 16 days after conception at a time when they were asymptomatic and serum levels of β-hCG in the normal range were increasing at an apparently normal rate. Serum progesterone and oestradiol levels were compared with those from normal women matched for gestational age and serum β-hCG levels whose singleton intrauterine pregnancies proceeded normally beyond 20 weeks. Mean serum progesterone levels were significantly lower in those women with ectopic pregnancy than in matched controls ($P \leq 0{\cdot}002$); however, there was no statistically significant difference seen between the serum progesterone levels in women conceiving blighted ovum pregnancies and matched controls ($P = 0{\cdot}187$). Furthermore, serum progesterone levels were significantly lower in ectopic pregnancies than blighted ovum pregnancies matched for hCG levels ($P < 0{\cdot}05$). Statistically significant differences were not seen in serum oestradiol levels between either group and matched controls. The low serum progesterone levels seen in ectopic pregnancy suggest that there is a specific and selective deficiency in progesterone synthesis which implies that factors other than hCG may influence luteal function in the earliest days of pregnancy.

# ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

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## MEETINGS AND COURSES IN 1992

| | |
|---|---|
| 29th-30th April | Educational Course<br>**Minimally Invasive Surgery** |
| 10th June | Scientific Meeting<br>**Prostaglandins and the Uterus** |
| 2nd-3rd July | Educational Course<br>**Colposcopy** (basic) |
| 7th-10th July | **British Congress in Obstetrics and Gynaecology**<br>(to be held in Manchester) |
| 13th-14th July | Postgraduate Meeting<br>**Safe Motherhood: The WHO Initiative and the RCOG** |
| 14th-16th July | Educational Course at Manchester<br>**Infertility** |
| 20th-24th July | **MRCOG Part I Intensive Theoretical Revision Course** |
| 15th-16th August | Joint Meeting of the RCOG and the<br>Danish Obstetric & Gynaecological Society<br>**Immunology in Obstetrics and Gynaecology**<br>(to be held in Copenhagen) |
| 15th-16th September | Educational Course<br>**Practical Urodynamics and Female Urinary Incontinence** |
| 9th-10th October | **Diplomates' Course for General Practitioners** |
| 28th October | Scientific Meeting<br>**Management of Infertility** |
| 30th November-<br>4th December | **Consultants' Conference** |

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# British Journal of Obstetrics and Gynaecology

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# British Journal of Obstetrics and Gynaecology

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Edited by Geoffrey Chamberlain

SUPER ARDUA

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# 6 reasons why more doctors prescribe Prempak-C and Premarin than any other HRT.

## ① 50 YEARS EXPERIENCE

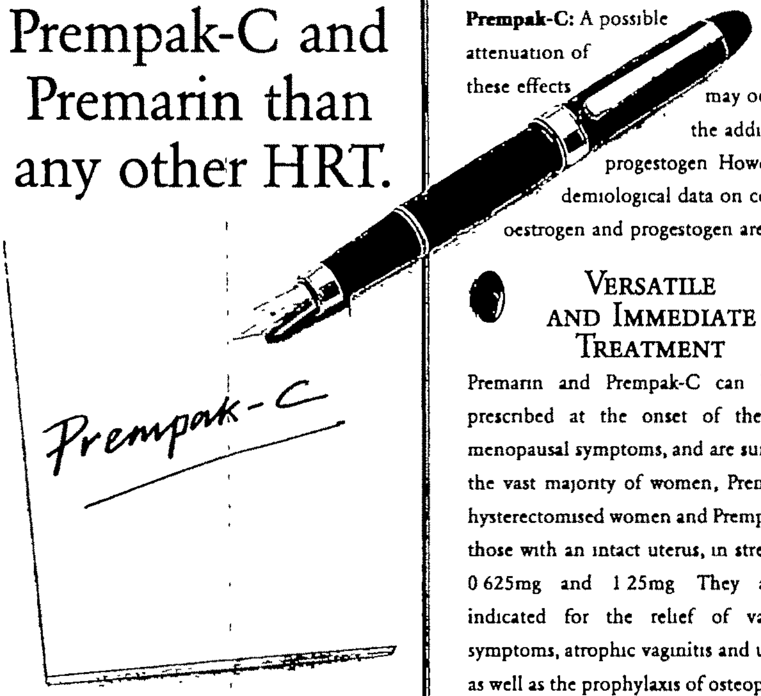
Premarin, a natural conjugated oestrogen, which is also used in the formulation of Prempak-C, is the only oestrogen used in any HRT with 50 years experience The majority of long term studies, therefore, relate to the conjugated oestrogen found only in these products.

## ② LONG TERM SAFETY - BREAST CANCER?

Both doctors and patients are justifiably concerned about the potential risks of breast cancer for women taking HRT. Whilst there is suggestive evidence of a small increased risk of breast cancer with long-term HRT (greater than 5 years), this varies with the type and dose of the oestrogen used. However, a recent comprehensive review of 31 studies provides evidence that menopausal therapy consisting of 0.625mg/day of conjugated oestrogens does not increase the risk of breast cancer.[1] Most studies, in fact, relate to conjugated oestrogen and so there is insufficient data to arrive at similar conclusions for any other regimen.

## ③ PROPHYLAXIS OF OSTEOPOROSIS

Prempak-C and Premarin are both indicated for the prophylaxis of osteoporosis in women at risk of developing fractures. A minimum daily dose of 0.625mg Premarin preserves bone mass, therefore reducing the risk of debilitating injuries such as hip fractures, by up to 66%.[2,3] Further estimates suggest that prescribing Premarin for at least 10 years will reduce the risk of mortality linked to osteoporosis by 60%.[4]



## ④ REDUCING CARDIOVASCULAR DISEASE RISKS

**Premarin:** A recent review of considerable epidemiological evidence has shown, overall, a 50% reduction in risk of coronary disease in oestrogen users The most common form of oestrogen used in all these studies was conjugated oestrogen, i e. Premarin

**Prempak-C:** A possible attenuation of these effects may occur with the addition of a progestogen However, epidemiological data on combined oestrogen and progestogen are limited

## ⑤ VERSATILE AND IMMEDIATE TREATMENT

Premarin and Prempak-C can both be prescribed at the onset of the earliest menopausal symptoms, and are suitable for the vast majority of women, Premarin for hysterectomised women and Prempak-C for those with an intact uterus, in strengths of 0 625mg and 1 25mg They are also indicated for the relief of vasomotor symptoms, atrophic vaginitis and urethritis, as well as the prophylaxis of osteoporosis in women at risk

## ⑥ COST EFFECTIVE

Treatment costs are becoming increasingly important, especially as long term therapy can last from 5 to 10 years or longer. Compared to other forms of HRT, Wyeth's products cost remarkably little, Premarin costs just £1.84 and Prempak-C costs £4.06, for 28 days of therapy[7]

PREMPAK-C

PREMARIN

## ABBREVIATED PRESCRIBING INFORMATION

**PREMARIN*** **USES:** Menopausal and post menopausal oestrogen therapy in women without a uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures

**DOSAGE AND ADMINISTRATION·** Natural conjugated oestrogens 0 625mg - 1 25mg daily Continuous administration is recommended In women with an intact uterus the addition of a progestogen for 10-12 days per cycle is essential

**CONTRA-INDICATIONS** Known or suspected pregnancy and during lactation History of known or suspected cancer of the breast Oestrogen dependent neoplasia Undiagnosed abnormal genital bleeding Active thrombophlebitis or thromboembolic disorders Acute or chronic liver disease Rotor or Dubin-Johnson syndrome. Severe cardiac or renal disease

**WARNINGS AND PRECAUTIONS.** Some studies have reported a small increased risk of breast cancer in long term oestrogen replacement therapy users (greater than 5 years), others however have not shown this relationship It is not known whether concurrent progestogen influences this risk The risk of endometrial hyperplasia and carcinoma with unopposed oestrogen use is lowered by the addition of a progestogen. Diseases that may deteriorate during therapy include otosclerosis, multiple sclerosis, systemic lupus erythematosis, porphyria, melanoma, epilepsy, migraine and asthma Use with caution in patients with pre-existing uterine fibroids, endometriosis, breast nodules, fibrocystic disease, and in those with a history of deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction, cardiac or renal dysfunction Discontinue if jaundice, migraine, visual disturbances, thromboembolic phenomena or significant hypertension develop Certain endocrine and liver function tests may be affected Rarely idiosyncratic hypertension may occur Discontinue treatment prior to surgery or prolonged immobilisation Gallbladder disease. Insulin requirements may be altered Premarin is not an oral contraceptive

**SIDE EFFECTS.** The following have been reported with oestrogen therapy premenstrual-like syndrome, increase in size of uterine fibromyomata, vaginal candidiasis, changes in cervical erosion and secretion, cystitis-like syndrome, breast changes, gastrointestinal symptoms, chloasma, melasma, erythema multiforme, erythema nodosum, haemorrhagic eruption, alopecia, hirsutism, steepening of corneal curvature, intolerance to contact lenses, headaches, migraine, dizziness, mental depression, chorea, weight changes, reduced carbohydrate tolerance, aggravation of porphyria, oedema, changes in libido, leg cramps

**PRODUCT LICENCE NUMBERS:** Premarin 0 625mg PL0011/0165 Premarin 1 25mg PL0011/0166 Premarin 2 5mg PL0011/0167 **BASIC NHS PRICE:** Premarin 0 625mg £1 84 (28 days) For full prescribing information please refer to data sheet

**PREMPAK-C** **USES:** Menopausal and postmenopausal oestrogen therapy for women with an intact uterus for vasomotor symptoms, allied disorders such as atrophic vaginitis, kraurosis vulvae, atrophic urethritis, and prophylaxis of osteoporosis in women at risk of developing fractures

**DOSAGE AND ADMINISTRATION:** Natural conjugated oestrogens 0 625mg - 1 25mg daily and one norgestrel 0 15mg tablet should be taken daily from day 17 to day 28 of oestrogen therapy

**CONTRA-INDICATIONS:** As for Premarin

**WARNINGS AND PRECAUTIONS** As for Premarin Prempak-C is not an oral contraceptive

**SIDE EFFECTS:** As for Premarin. Breakthrough bleeding and spotting Change in menstrual flow, dysmenorrhoea, amenorrhoea

**PRODUCT LICENCE NUMBERS** Prempak-C 0 625mg PL0011/0161 Prempak-C 1 25mg PL0011/0162

**BASIC NHS PRICE:** £4 06 - 28 days For full prescribing information please refer to data sheet

**REFERENCES** 1 Dupont W D and Page D L. (1991) Arch Int Med 151, 67-72 2 Lindsay R et al (1984) Obstet Gynecol. 63, 759-763 3 Kiel D P et al (1987) NEJM, 317, 1169-1174 4 Ross R K et al (1989) Lancet, 1, 505 5 Stampfer M J and Colditz G A (1991) Prev Med, 20, 47-63 6 Stampfer M.J et al (1991) NEJM, 325, 756-762 7 MIMs June 1992

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**PREMARIN***
(Conjugated Oestrogens)

Wyeth Laboratories, Huntercombe Lane South,
Taplow, Maidenhead, Berkshire SL6 0PH.

**PREMPAK-C***
(Conjugated Oestrogens + Norgestrel)

# British Journal of Obstetrics and Gynaecology

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Letters to the editor are published only if they comment usefully on material published in previous issues. Letters should not exceed 400 words and must be typed with double line-spacing.

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Tables and figures should be separate from the text, with their positions indicated in the text margin. Both are numbered with arabic numerals. Coloured illustrations are used sparingly when these appreciably improve clarity.

Figures should be marked on the back (lightly in pencil) only with the name of the paper, the figure number and to indicate the top. Each should have a descriptive legend typed on a sheet separate from the figure. Photographs should be unmounted glossy bromide prints of good contrast.

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Some points of detail to note are:

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(2) The use of confidence intervals is encouraged
(3) The symbol ± should not be used when presenting SE or SD. Presentation such as 'the mean . . was 14·2 (SD 3·2) mg' is preferred.
(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences.
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British Journal of Obstetrics and Gynaecology
September 1992, Vol. 99, pp. 707–710

## COMMENTARIES

# Should we try to supplement the growth retarded fetus? A cautionary tale

It is only five years since Peter Soothill *et al.* (1987) published their seminal paper on the metabolic state of the growth retarded human fetus. In late 1991, the First International Symposium of Perinatal Medicine was held in Tokyo and provided an opportunity to review the implications of the subsequent explosion of our knowledge of the metabolic state of the growth retarded human fetus in relation to similar data from experimental animals and the possibilities for clinical intervention that this knowledge provides.

Intrauterine growth retardation, both human and in experimental animals, is characterized by fetal hypoglycaemia and hypoxaemia, at least in late gestation (Soothill *et al.*, 1987; Owens *et al.*, 1989; Harding & Charlton, 1990). Animal experiments have shown that consumption of both glucose and oxygen by the growth retarded fetus is similar per unit weight to that of the normally grown fetus, suggesting that fetal growth rate may be limited by the supply of these substrates (Owens *et al.*, 1987*a,b*). However, in sheep fetal supply is maximized as far as possible in growth retardation by a large reduction in placental glucose and oxygen consumption. In order to maintain placental function despite this reduction, there are dramatic changes in amino acids metabolism within the uterus. Late in pregnancy the fetus, which has previously been receiving amino acids across the placenta, begins to lose amino acids back to its placenta and thus to waste away. This loss of amino acids is selective, with alanine and the branched-chain amino acids making the greatest contribution (Owens, 1991). The growth retarded human fetus has lowered concentrations of amino acids in its blood, and again alanine and the branched-chain amino acids show the greatest changes (Cetin *et al.*, 1988; Economides *et al.*, 1989). In Tokyo, Cetin and her colleagues presented elegant studies using stable isotopes which, together with their data from cordocentesis and cord blood samples, suggest that the human fetus may also lose the branched-chain amino acid, leucine, to the placenta. Earlier work has shown that when placental function is likely to be compromised, the human placenta is able to utilize this nutrient source (Bloxam *et al.*, 1987). Ultrasound evidence that the abdominal circumference of the growth retarded fetus may decrease with increasing gestational age (Divon *et al.*, 1986) also suggests the human growth retarded fetus may waste away in late pregnancy to sustain both its own energy metabolism and that of its placenta.

In Tokyo, we reviewed the possibility that this new information on substrate deprivation of the growth retarded fetus may be applied to intervene clinically by intrauterine supplementation after a diagnosis of intrauterine growth retardation has been made. Two important areas were discussed. Firstly, there is little evidence that such supplements will actually alter fetal growth. In one series of experiments, direct intravenous or intragastric supplements of glucose and amino acids to fetal sheep prevented the development of growth retardation when begun at the same time as the growth retarding insult (maternal undernutrition or placental embolization, Charlton & Johengen, 1985, 1987). However, this does not mean that preexisting growth retardation can necessarily be reversed by supplements, or that growth retardation of differing causes will react in the same way. In fetal sheep, growth slows with the onset of maternal undernutrition, but resumes promptly on maternal refeeding only if the undernutrition has been of brief duration. If undernutrition is prolonged (greater than 21 days), maternal refeeding has no effect on fetal growth and the growth retardation appears to be irreversible (Mellor & Murray, 1982). This may be analogous to the growth retarded human neonate who fails to show catch-up growth postnatally and has long term irreversible growth failure. The mechanisms which determine the reversibility of changes in fetal growth are as yet unknown, but are clearly critical to the possible usefulness of intrauterine supplementation.

Secondly, there is evidence, both human and experimental, to suggest that supplementation may not be safe. Normally grown human fetuses given extra (and possibly excess) glucose by intravenous infusion to the mother may develop acidaemia within a few hours (Lawrence *et al.*, 1982; Kenepp *et al.*, 1982). Animal experiments suggest that this may be because increased fetal glucose supply causes an obligatory increase in fetal oxygen consumption with an accompanying decrease in fetal pO2 and increase in lactate concentration (Philipps *et al.*, 1984). Such effects may prove life threatening in the growth retarded fetus whose oxygenation is already marginal. Indeed, direct glucose infusion to the growth retarded human fetus has already been shown to cause a fall in fetal pH (Nicolini *et al.*, 1990). Glucose supplements to pregnant sheep carrying severely growth retarded fetuses also resulted in fetal death within days of instituting this treatment.

Amino acid supplementation is also not without risk. Amino acid supplements to normally grown fetal sheep caused a rise in fetal ammonia and urea concentrations and a fall in pO2 and pH (Charlton & Johengen, 1984). Evidence of similar changes has been reported in human infants delivered after maternal intravenous amino acid supplements (Benny *et al.*, 1978). The adverse effects of high levels of specific amino acids *in utero* are well known, such as in maternal phenylketonuria. High protein diets in pregnant rats, especially when the balance of amino acids is altered, actually inhibit fetal growth, apparently

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because the excess amino acids compete for uptake with other essential amino acids (Metcoff *et al.*, 1981).

Furthermore, high protein dietary supplements in human studies have been associated with only small or no gain in birthweight (Rush, 1989), but with an excess of preterm delivery and perinatal death, particularly when the normal diet of the supplemented women was not protein deficient and when a prior low birthweight infant had been delivered (Stein *et al.*, 1978). Cordocentesis will enable future investigators to identify the fetus which is hypoglycaemic or amino acid deficient *in utero* and test the effect of supplementation to restore concentrations to normal. However, it will require carefully designed prospective trials of sufficient magnitude to avoid both Type I and Type II errors before it will be possible to judge whether this should become a therapeutic option for treatment of the growth retarded human fetus. In addition, investigators should be mindful of the possible development of deficits in other macro and micronutrients following such supplementation, if it restores fetal growth and hence demand.

Initially, oxygen supplementation seems more attractive than nutrient supplementation, as few obstetricians would consider it potentially harmful. An increase in the margin of safety between supply of and demand for oxygen by the fetus may reduce the risk of death *in utero*, if not restore growth. However, once again experimental data derived from sheep sounds a note of caution. Oxygen supplements to pregnant sheep restored fetal pO2 to normal in moderately but not in severely growth retarded fetuses >2 and >5 SD, respectively, below the mean weight of controls). Furthermore, oxygen supplements in sheep failed to increase fetal oxygen consumption, suggesting the fetus was unable to utilize the additional oxygen. More worryingly, cessation of supplementation was followed by a period when fetal oxygenation was worse than it had been before the supplements were started. This would provide an explanation for the recent 'surprising observation' of an 'increase of the number of heart rate decelerations after discontinuation of maternal hyperoxia' in growth retarded fetuses (Bekedam *et al.*, 1991).

How safe, then, is intermittent maternal oxygen administration, either therapeutic or diagnostic? What if the woman wishes to stop her oxygen treatment to smoke a cigarette? Doppler studies in the human fetus which is also hypoglycaemic show that maternal oxygen supplements also increase cerebral and decrease peripheral vascular resistance (Arduini *et al.*, 1988). If this means diversion of an already scarce supply of glucose away from the fetal brain, oxygen supplementation may be far from the benign intervention that has been assumed.

We can only conclude that we should hasten slowly. Although we have made great progress in understanding the metabolic deficiencies of the growth retarded fetus, there is not yet good evidence that supplementation to treat such deficiencies is of benefit to any growth retarded fetus, and if so, to which. Futhermore, there is substantial evidence that supplements are associated with considerable risks. It is imperative that obstetricians await the results of randomized controlled trials, such as are already promised (Nicolaides *et al.*, 1987). Since most centres could only contribute a few cases each year, it would be appropriate to consider multicentre trials. Obstetricians should not consider offering supplements to their patients until such studies are published and show clear benefit. Perhaps the first promised one will be presented at the Second International Perinatal Conference in Italy in 1993.

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# WHO appropriate technology for birth revisited

In August 1985 *The Lancet* published the WHO recommendations for birth in an article entitled 'Appropriate technology for birth'. This publication followed the appearance, in the same year, of the WHO book, *Having a Baby in Europe*, which described the current status of childbirth care in Europe. Both these publications resulted in controversy as to their validity. In many, if not most, parts of Europe as well as in other regions this controversy continues.

Questions such as: How were the publications arrived at? How representative are their contents? Are these biased, 'liberal' views? And, most importantly, how well do these recommendations match up to research findings?

## Development of the WHO recommendations for birth

The United Nations declared 1979 as the International Year of the Child. At the Regional Committee for Europe in that year, concern was expressed over a number of issues including: the rapidly expanding technology being applied to birth with its associated rising costs; the doubling or even tripling of the caesarean section rate which took place in the 1970s, the question of whether this was associated with the increasing use of electronic fetal heart rate monitoring; the increasing demands from women's groups to resume control over their birth experiences and the poorly understood inequities relating to perinatal mortality (Wagner, 1991).

The outcome of this debate was a decision by the WHO to undertake research into perinatal services and to develop recommendations for appropriate technology for birth.

A series of events followed. The first was the establishment of a multidisciplinary, 15-member, perinatal study group. This consisted of representatives from obstetrics, paediatrics, nursing, midwifery, epidemiology and statistics, health administration, sociology, psychology, anthropology, economics and consumer groups. Meeting at least once a year as a full group, and more frequently in subgroups, the team investigated the available literature, the perinatal services in 23 of the then 32 WHO–Europe member states, mother–infant contact practices in a detailed study of ten representative member states and alternate (meaning outside of the formal health care system) perinatal services in Europe, as well as in the USA and Canada (Wagner, 1991).

Debate and eventual consensus between the members of the team resulted in *Having a Baby in Europe* (WHO, 1985). This was directed towards lay readers; *Perinatal Health Services in Europe Searching for Better Childbirth* (WHO, 1985) was aimed at the academic reader.

The second major step in the process followed: the organisation of Birth Conferences. These were national conferences designed to debate the applicability of the recommendations of the WHO books to a country. These conferences have almost always involved professionals and consumer groups as well as non-governmental organizations and the media. To date 43 conferences have been held in 23 European member states, as well as in the USA, Canada, Australia and China (Wagner, 1991).

The birth conference movement led to three major inter-regional meetings. These, combining in particular the WHO areas of Europe and America, covered appropriate technology for pregnancy, for birth and for after the birth. These conferences always involved multidisciplinary representation and required participants to submit their papers well in advance to enable translation and circulation before the meeting. At the conference issues were debated until consensus was reached. The outcome of these deliberations was published in the *Lancet* (WHO, 1985).

## How valid are these recommendations?

There is no doubt that much deliberation, research and discussion went into the development of the WHO recommend-

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**Table 1.** WHO recommendations for birth classified according to Chalmers *et al.* (1989).

| WHO Recommendations | Chalmers *et al.* (1989) |
|---|---|
| The well-being of the new mother must be ensured through free access of a chosen member of her family during birth and throughout the postnatal period. In addition, the health team must provide emotional support. | Enhanced social and psychological support from care givers reduces negative outcomes. Leaving women unattended during labour should be abandoned. |
| Women must participate in decisions about their birth experiences. | Failing to involve women in decisions about their care should be abandoned. |
| The healthy newborn must remain with the mother whenever possible. | Separating healthy mothers and babies routinely should be abandoned. |
| Immediate breast feeding should be encouraged even before the mother leaves the delivery room. | Unrestricted mother–infant contact after delivery and unrestricted breast feeding reduce breast feeding failure. |
| There is no justification to have a caesarean section rate of higher than 10–15%. Vaginal deliveries after a caesarean section should be encouraged. | Repeating caesarean section routinely after previous caesarean section should be abandoned. (There is little improvement in outcome with rates above 7%.) |
| Electronic fetal monitoring should not be routine. | Routine continuous monitoring of fetal heart rate without fetal scalp blood sampling should be abandoned. |
| There is no indication for shaving pubic hair before delivery. | Shaving the perineum routinely should be abandoned. |
| There is no indication for routine enemas before delivery. | Administering enemas or suppositories routinely should be abandoned. |
| The dorsal lithotomy position during labour and delivery is not recommended. Women must decide which position to adopt for delivery. | Restricted maternal position during labour and delivery should be abandoned Upright versus recumbent position during first and second stage reduces negative outcome. |
| Systematic use of episiotomy is not justified. | Performing episiotomy routinely should be abandoned. |
| Induction of labour should be reserved for specific medical indications. | Inducing labour routinely at less than 42 weeks gestation should be abandoned. |
| The routine administration of analgesic or anaesthetic drugs should be avoided. | Prescribing sedatives or tranquilizers routinely should be abandoned. |
| Artificial early rupture of membranes, as a routine process, is not justifiable. | Amniotomy to augment spontaneous labour appears promising but requires further evaluation. |

ations for appropriate technology at birth. Nevertheless, some questions persist. How valid are these recommendations? How representative were the participants in the various conferences and research teams? Is it not possible, if not probable, that individuals willing to participate in such meetings and activities would have an interest in 'changing the system' and would be biased? Most important, how well do the recommendations match up to research findings?

The recent publication by Chalmers, *et al* (1989) encompassing a careful scrutiny of randomized control trials of perinatal technology allows these questions to be answered. This two volume tome contains many reviews of great value but of particular relevance here are the four appendices. These list the forms of perinatal technology that (a) reduce the negative outcomes of pregnancy and childbirth; (b) are promising but require further evaluation; (c) have unknown effects and require further evaluation; and (d) should be abandoned in the light of the available evidence.

The WHO recommendations for appropriate technology for birth are examined in Table 1 in terms of their classification by Chalmers *et al.* (1989). This appendix deals only with the specific birth technology recommendations and does not assess the general recommendations regarding perinatal health care policy and the setting of policy.

The recommendations of the WHO for appropriate technology at birth, developed through survey research, discussion and debate, are strongly endorsed by the findings of carefully controlled and critically evaluated randomized control trials. The recommendations provide sound guidance for those providing perinatal care.

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# A case-control study of unexplained antepartum stillbirths

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## ABSTRACT

**Objective** To ascertain factors that will identify women who are at increased risk of unexplained antepartum stillbirth.

**Design** Matched case-control study. The cases and controls were initially analysed as a whole group and again after dichotomizing into those of low birthweight (<2500 g) and those of normal birthweight (≥2500 g).

**Setting** Western Australia 1980–1983.

**Subjects** Unexplained antepartum stillbirths of ≥1000 g birthweight (cases) and liveborn infants individually matched for year of birth, plurality, sex and birthweight of infant and race of mother (controls).

**Results** The case pregnancies had more polyhydramnios (OR 10·83, 95% CI 2·41–48·69) and cord problems (OR 6·57 95% CI 1·36–31·75) than the controls but, paradoxically, other obstetric and medical complications were less common in the cases. The association with polyhydramnios persisted when the analysis was confined to those with low birthweight. With normal birthweight fetal distress was more frequent in the cases (OR 3·65 95% CI 1·36–9·80) but there were few other differences.

**Conclusions** The clinical and diagnostic systems currently in use are unable to identify many fetuses at risk of death. Decreases in the rate of unexplained antepartum stillbirths await the discovery of new preventable causes, or of innovations in clinical or laboratory aspects of obstetric care.

Most of the stillbirths which occur today in developed countries are antepartum (Cole 1989). A large proportion of these deaths has no apparent cause and unexplained antepartum stillbirths are now a major contributor to perinatal mortality (Editorial 1987; Yudkin *et al.* 1987; Grant *et al.* 1989; Cole 1989). Therefore, they form a group which deserves particular attention in terms of research and possible preventive action. The extent to which unexplained antepartum stillbirths can be prevented by current antenatal care is limited and attempts at prevention, such as fetal movement counting, have been unsuccessful (Grant *et al.* 1989). It has been suggested that until more is known about the underlying pathological processes and a method is developed of successfully interrupting them, case-control studies should be carried out to investigate these deaths (Dickson *et al.* 1988; Chalmers 1989).

Between 1980 and 1983 there were approximately 22 000 births per year in Western Australia, approximately 6% were low birthweight (<2500 g) and approximately 1% were very low birthweight (<1500 g). The stillbirth rate over this period was 7·0 per 1000 total births (excluding births weighing <500 g). Stillbirths under 1000 g were excluded from this study for reasons explained in the methods. For stillbirths ≥1000 g, the rate was 4·8 per 1000 total births and the antepartum and intrapartum rates were 3·3 and 1·2 respectively;

68·8% of these stillbirths were antepartum, 25·8% were intrapartum and the time of death could not be determined for the remaining 5·4%.

In this paper, we present a case-control study comparing the unexplained antepartum stillbirths with a liveborn control group matched for birthweight and in the following paper (Alessandri *et al.* 1992) we investigate the intrapartum stillbirths. The purpose of the study was to ascertain risk factors for antepartum stillbirth of unknown cause in a total population. Specifically, we aimed to determine whether any antenatal characteristics could be detected more commonly in pregnancies ending in unexplained antepartum stillbirth than in those where the infants were liveborn controls. These characteristics could then be tested for their usefulness as markers for intensive fetal surveillance.

## Subjects and methods

### *Definitions*

In Western Australia, stillbirth (fetal death) is defined as the birth of a fetus of at least 20 weeks gestation or 400 g birthweight which shows no sign of life after birth. An antepartum stillbirth is one in which the heart beat ceased before labour, and an intrapartum stillbirth is one in which the heart beat ceased during labour. Stillbirth rates are calculated per 1000 total births, excluding all births <500 g birthweight. This definition of stillbirth rates conforms with that of the World Health Organization (Chiswick 1986).

### *Case selection*

All antepartum stillbirths weighing ≥1000 g born in Western Australia between 1980 and 1983 inclusive were ascertained from perinatal death certificates collected by the Registrar-General. These certificates contain demographic details of the mother and baby together with information on the cause of death. The stillbirth cases were also identified in the computer files of the Western Australian Midwives' Notification System (Gee 1990). As a statutory requirement, a notification form is completed by the attending midwife for every live and still birth in Western Australia with a birthweight of ≥400 g or a gestational age of ≥20 weeks. The data collected include demographic details of the mother, information on pregnancy, labour and delivery and other particulars relating to the baby. Ascertainment of cases began in 1985 and data collection in 1986. As this was an extensive study in terms of data collection, including the perusal of both hospital and doctors' records from all areas of Western Australia, completion of data coding was not finalized until 1990.

Stillbirths of <1000 g were excluded from the study as there was a specific interest in those infants who were in birthweight categories where there was a reasonable chance of survival. In addition, the classification of fetuses under 1000 g as 'abortion', 'stillbirth' or 'early neonatal death' is often difficult and may vary with the medical practitioner and social circumstances. Also, birthweight and gestational age are often recorded inaccurately and stillbirths are less likely to be registered when the birthweight is below 1000 g.

Information relating to the mother and baby (such as maternal age and parity, infant birthweight and gestational age) was obtained from both sources—perinatal death certificates and midwives' notification forms. Where the same data were recorded on both data sources, data from the midwives' notification system were used because it was considered that these data were more reliable (Hill 1987). Cause of death and the timing of cessation of fetal heart beat were obtained only from perinatal death certificates.

Most of the items on the midwives' forms are collected accurately with the exception of gestational age. On the midwives' form, gestational age is calculated from the first day of the mother's last menstrual period, or from the expected date of delivery when accurate menstrual data are unavailable. In this study, a 'best' estimate of gestational age was obtained from a certain date of last menstrual period where available, antenatal ultrasound examinations and clinical assessments of uterine size as well as any available paediatric assessments.

In antepartum stillbirth, death may have occurred several weeks before birth so that gestational age at birth would overestimate the 'true' gestational age at death. An attempt was made to estimate gestational age at death for cases by perusing information on the cessation of fetal heart beat from perinatal death certificates and data on fetal movements from the medical record. A new variable, referred to as 'adjusted gestational age', was created using this gestational age at death for cases and gestational age at birth for controls.

The causes of death given on perinatal death certificates may be unreliable (Wigglesworth 1980; Stanley & Waddell 1985; Lammer *et al.* 1989). To overcome this, primary causes of stillbirth in this study were grouped according to our own classification system (Alessandri *et al.* 1988). The 'unknown' category not only included those stillbirths where the primary cause of death on the perinatal death certificate was recorded as unknown but also included death certificate primary causes which were unlikely to be 'true' reasons for death *in utero*, such as cord around neck or anoxia/asphyxia. The antepartum stillbirths in this 'unknown' category formed the case group for the study and are referred to as unexplained antepartum stillbirths.

Post mortems were performed on 66·2% of all antepartum stillbirths and 70·1% of unexplained antepartum stillbirths. In Western Australia, perinatal death certificates are updated with post mortem information. Due to the retrospective nature of this study, the cause of death information on death certificates should have included any relevant post mortem details.

All stillbirths were also checked against the Western Australian Congenital Malformations Register (Bower & Stanley 1983). This was to ensure that there were no stillbirths with lethal malformations in the 'unknown' category as determined from the perinatal death certificates. Two additional antepartum stillbirths with lethal malformations which had not been identified from the death certificates, and had originally been classified as cause of death unknown, were consequently excluded from this analysis.

### *Control selection*

Controls were selected from the computer files of the midwives' notification system. Two controls per case were matched for year of birth, plurality, sex, birthweight and race of mother. Controls were livebirths that had survived the neonatal period. Neonatal deaths were excluded from the controls by manual checking with the death files of the Australian Bureau of Statistics. Those controls found to be neonatal deaths were replaced by other suitably matched neonatal survivors. As with cases, information relating to the mother and baby was obtained from the midwives' notifications for each control in the study.

Matching for birthweight was carried out because a number of known risk factors for stillbirth are thought to be mediated through low birthweight (LBW) and approximately 50% of the cases were in the LBW range (< 2500 g). There was a particular interest in the differences between infants who died *in utero* and those with similar birthweights who survived. It was impossible to match birthweights exactly, therefore the first control was matched within 100 g and the second was matched within 200 g. Birthweight matching proved to be difficult for some cases under 2000 g. Thus, for 13 cases, suitable birthweight matches could not be found in the appropriate year of birth so that two first controls and 13 second controls were not matched on the year of birth variable. Ten of these controls were obtained from the birth year 1979 and the other five were mismatches within the study years of birth.

Matching for sex and plurality was undertaken because males and females and singletons and multiples have different birthweight distributions. The matching for race involved matching only for Aboriginality so that Aboriginal births were matched with other Aboriginal births and non-Aboriginals with other non-Aboriginals. Controls were matched on race because the stillbirth rate for Aboriginals is much higher than for non-Aboriginals (Seward & Stanley 1981; Gogna *et al.* 1986; Alessandri *et al.* 1988) and, while nearly 6% of livebirths in Western Australia are to Aboriginal mothers, 12% of stillbirths are Aboriginal (Gee 1990).

### *Data collection*

In addition to the information obtained from the midwives' notifications, data relating to past obstetric history, associated medical conditions, index pregnancy characteristics, blood pressure before labour (see Hughes 1972) and antenatal hospital admission(s) were collected for each case and control in the study. These data were obtained from hospital records. Where the necessary antenatal information could not be obtained from hospital records it was sought from doctors' records. For some mothers, a number of doctors needed to be contacted before the antenatal information could be obtained. Some doctors would not comply with the request for data irrespective of how many times they were contacted.

Despite these problems, the required antenatal records were obtained for approximately 70% of the total study population, comprising 70% of the unexplained antepartum stillbirths and 73% of the matched controls. The only difference between those for whom antenatal data were obtained and those for whom data were not, related to area of residence (of records obtained 30% of mothers were rural residents compared with 43% rural residents for those records not obtained). When investigating case/control status with regard to antenatal records obtained or not obtained, none of the variables reseached (including area of residence) showed differences which would significantly affect the study findings.

While collecting data from hospital records, the information obtained from the midwives' files was also checked and it was discovered that there were a few discrepancies for birthweight, race and sex. As these were matching variables, these discrepancies led to the exclusion of four controls so that four cases had only one control instead of two.

### *Analysis*

The analysis for this paper involved comparing unexplained antepartum stillbirths with their birthweight matched controls for a number of pregnancy and medical variables using conditional logistic regression. Initially, the cases and controls were analysed as a whole group and then dichotomized on the basis of birthweight and two separate analyses were performed. One analysis compared those cases having birth weights <2500 g with their corresponding controls and the other compared cases with birthweights of ⩾2500 g with their matched controls.

The data were analysed by means of the Egret software package (Epixact, version 0·02, 1985–1989, Serc & Cytel, Seattle, Washington). For all analyses the results are given in terms of odds ratios, their 95% confidence intervals (CI) and *P*-values. A *P*-value of <0·05 was regarded as being of statistical significance. The odds ratio was the ratio of the proportion of unexplained antepartum stillbirths with a particular pregnancy or medical variable to the proportion of controls with that variable. Thus, odds ratios below 1 suggested that the variable was present less often in unexplained antepartum stillbirths than in the matched controls compared with the nominated baseline, and odds ratios above 1 suggested that the variable was present more often in unexplained antepartum stillbirths than controls.

The baseline for most of the variables shown in the results tables was taken as the absence of the particular pregnancy or medical variable being analysed. For example, for bleeding before 20 weeks and polyhydramnios, the baselines were no bleeding before 20 weeks and no polyhydramnios, respectively. However, the number of 'other' problems in pregnancy, average weekly maternal weight gain, mean arterial pressure in the second and third trimesters and maximum systolic and diastolic blood pressures during pregnancy were analysed as continuous variables. Odds ratios below 1 for these variables implied that the controls had higher values than cases; for example, higher maximum systolic blood pressures or higher numbers of 'other' problems in pregnancy, and odds ratios above 1 suggested that cases had higher values than controls.

## Results

The proportion of antepartum stillbirths ($n = 294$) that were unexplained was 59·2%. Hence, there were 174 unexplained antepartum stillbirths (cases) in the study population and 344 matched controls (174 first controls and 170 second controls). For the dichotomized analyses, there were 95 cases with birthweights <2500 g and 187 corresponding controls forming the LBW group and 79 cases of birthweight ⩾2500 g and 157 corresponding controls comprising the normal birthweight group. In all analyses, unexplained antepartum stillbirths were compared with controls for pregnancy and medical variables

**Table 1.** Odds ratio, 95% CI* and $P$-values for total unexplained antepartum stillbirths compared with controls, Western Australia 1980–1983: obstetric history, medical and pregnancy problems in index pregnancy.

| Variables | Odds ratio | (95% CI*) | $P$-value |
|---|---|---|---|
| Past obstetric and medical history | | | |
| Past history of hypertension | 0·61 | (0·29–1·30) | 0·203 |
| ⩾1 previous miscarriage | 0·62 | (0·38–1·03) | 0·064 |
| ⩾1 'other' maternal medical disorders | 0·40 | (0·20–0·79) | 0·008 |
| Index pregnancy characteristics and problems | | | |
| Bleeding <20 weeks | 0·19 | (0·07–0·55) | 0·002 |
| Bleeding ⩾20 weeks | 0·32 | (0·15–0·66) | 0·002 |
| Prelabour rupture of membranes | 0·18 | (0·08–0·40) | <0·001 |
| Number of 'other' problems in pregnancy† | 0·62 | (0·50–0·78) | <0·001 |
| Prolonged rupture of membranes | 0·11 | (0·01–0·80) | 0·030 |
| Urinary tract infection | 0·76 | (0·51–1·14) | 0·182 |
| Cervical sutures and/or threatened preterm labour | 0·10 | (0·01–0·78) | 0·028 |
| Placental bleeding | 0·29 | (0·08–1·01) | 0·052 |
| Evidence of fetal distress‡ | 0·98 | (0·53–1·83) | 0·958 |
| Pre-eclampsia | 0·39 | (0·18–0·83) | 0·015 |
| Polyhydramnios | 10·83 | (2·41–48·69) | 0·002 |
| Cord abnormalities | 6·57 | (1·36–31·75) | 0·019 |
| Average weekly maternal weight gain | 1·27§ | (1·06–1·51) | 0·007 |
| (i) Blood pressure | | | |
| Mean arterial pressure in 2nd trimester | 0·94¶ | (0·65–1·34) | 0·717 |
| Mean arterial pressure in 3rd trimester | 0·97¶ | (0·72–1·29) | 0·819 |
| Rise in blood pressure from 1st antenatal visit | 0·82 | (0·53–1·28) | 0·390 |
| Maximum systolic blood pressure | 0·90‖ | (0·79–1·03) | 0·130 |
| Maximum diastolic blood pressure | 0·87** | (0·73–1·03) | 0·113 |
| Reliability of blood pressure data | 0·95 | (0·55–1·63) | 0·854 |
| Antihypertensive therapy | 0·13 | (0·03–0·55) | 0·006 |

* CI = Confidence interval.

† Included conditions such as urinary tract infections, viral or other infections, prolonged rupture of membranes, threatened preterm labour and venereal infections.

‡ Defined as recorded in the medical notes, usually meconium stained amniotic fluid or abnormal cardiotocography.

§ Odds ratio change of 100 g/week of average weekly maternal weight gain.

¶ Odds ratio change of 10 mmHg of blood pressure.

‖ Odds ratio change of 10 mmHg or systolic blood pressure.

** Odds ratio change of 10 mmHg of diastolic blood pressure.

of interest. The pregnancy and medical data comprised the mothers' past obstetric history, associated medical conditions and index pregnancy characteristics and problems including extensive data on maternal blood pressure. For the groups dichotomised by birthweight, only variables which were significantly different ($P<0·05$) between cases and controls were tabulated. However, the results for all pregnancy and medical variables analysed were tabulated for the total case-control population. Frequencies for variables shown in the results tables are given in the Appendix.

In addition to the pregnancy and medical variables, maternal age, parity and antenatal care (gestation at first visit and number of antenatal visits controlling for gestation) were also analysed. No significant differences were observed between cases and controls for any of these variables.

### *(1) Past obstetric history*

Although data were gathered on a past history of infertility, postpartum haemorrhage, retained placenta and caesarean sections, the number of individual women with these conditions was too small to perform specific analyses. There were adequate numbers of women with a history of known previous miscarriages and also with a past history of hypertension. Although the difference was not significant, there were more controls than unexplained antepartum stillbirths with one or more previous miscarriages, the $P$-value being close to significance (Table 1).

### *(2) Associated medical conditions*

The numbers of women with medical conditions such as chronic renal disease and heart disease were also too small for analysis (eight mothers, all controls, had chronic renal disease while four case mothers and four control mothers had heart disease). Gestational diabetes and diabetes mellitus were also not analysed for the same reason (a total of four mothers, two with stillbirths and two mothers of controls may have had untreated gestational diabetes; there were also four women, all mothers of controls, with diabetes mellitus). There were significantly more mothers of controls than mothers of unexplained antepartum stillbirths with one or more 'other' medical disorders (Table 1), ('other' included conditions such as thyroid disease, asthma, epilepsy, mental disorders, rheumatoid

**Table 2.** Odds ratio, 95% CI and $P$-values for low birthweight unexplained antepartum stillbirths compared with controls, Western Australia 1980–1983: medical and pregnancy problems in index pregnancy.

| Variables | Odds ratio | (95% CI) | $P$-value |
|---|---|---|---|
| One or more 'other' maternal medical disorders | 0·35 | (0·15–0·81) | 0·015 |
| Bleeding <20 weeks | 0·06 | (0·01–0·44) | 0·006 |
| Bleeding ≥20 week | 0·22 | (0·09–0·54) | <0·001 |
| Prelabour rupture of membranes | 0·15 | (0·05–0·42) | <0·001 |
| Number of 'other' problems in pregnancy† | 0·41 | (0·29–0·58) | <0·001 |
| Prolonged rupture of membranes | 0·11 | (0·01–0·80) | 0·030 |
| Placental bleeding | 0·10 | (0·01–0·78) | 0·028 |
| Evidence of fetal distress‡ | 0·30 | (0·10–0·89) | 0·029 |
| Pre-eclampsia | 0·14 | (0·04–0·49) | 0·002 |
| Polyhydramnios | 8·84 | (1·92–40.7) | 0·005 |
| Maximum systolic blood pressure | 0·84§ | (0·71–0·99) | 0·047 |
| Maximum diastolic blood pressure | 0·78¶ | (0·62–0·97) | 0·029 |
| Antihypertensive therapy | 0·07 | (0·01–0·52) | 0·010 |

† Included conditions such as urinary tract infections, viral or other infections, prolonged rupture of membranes, threatened preterm labour and venereal infections.

‡ Defined as recorded in the medical notes, usually meconium stained amniotic fluid or abnormal cardiotocography.

§ Odds ratio change of 10 mmHg of systolic blood pressure.

¶ Odds ratio change of 10 mmHg of diastolic blood pressure.

arthritis and obesity). This significant finding was also observed in the LBW group (Table 2).

### *(3) Index pregnancy characteristics and problems*

Analysis of pregnancy problems and characteristics revealed many significant differences between mothers of unexplained antepartum stillbirths and mothers of controls. In general, the mothers of controls were more likely to have had pregnancy problems than those of unexplained antepartum stillbirths. Significantly more mothers of controls than cases had bleeding before 20 weeks (threatened miscarriage), bleeding at 20 or more weeks (antepartum haemorrhage), prelabour rupture of membranes, 'other' problems in pregnancy considered as a group (included such conditions as urinary tract infections, viral or other infections, prolonged rupture of membranes, threatened preterm labour and venereal infections), prolonged rupture of membranes and cervical sutures and/or threatened preterm labour considered as individual factors and pre-eclampsia (Table 1). The LBW group showed similar results but also had significantly more mothers of controls than cases with placental bleeding, and evidence of fetal distress (defined as recorded in the medical notes, usually meconium stained amniotic fluid or abnormal cardiotocography) (Table 2). In the normal birthweight group there were significantly more mothers of controls than cases only for prelabour rupture of membranes (Table 3).

There were two pregnancy conditions which were significantly more frequent in mothers of unexplained antepartum stillbirths than in those of controls—these were polyhydramnios and 'cord abnormalities' (twisting, spiralling) (Table 1). Mothers of unexplained antepartum stillbirths also had a significantly higher average weekly weight gain than mothers of controls (Table 1). Investigations of the data showed that this was not associated with polyhydramnios. In the LBW group there were also significantly more mothers of cases than controls with polyhydramnios (Table 2). The normal birthweight group, however, had significantly more mothers of cases than controls with evidence of fetal distress (Table 3). Both in the LBW and normal birthweight groups, mothers of cases tended to have higher average weekly weight gains than mothers of controls, the $P$-values being just outside the specified significance level (LBW group—$P$ = 0·059; normal birthweight group—$P$ = 0·055).

(i) Blood pressure: Data on a number of variables relating to blood pressure were analysed. These included mean arterial pressures in the second and third trimesters, the presence of a rise in blood pressure from the first antenatal visit, maximum systolic blood pressure during pregnancy, maximum diastolic blood pressure during pregnancy, the reliability of blood pressure data and use of anti-hypertensive drug therapy. The only significant result obtained was that significantly more mothers of controls received anti-hypertensive drug therapy than did mothers of cases (Table 1).

This was also observed in the LBW group but, in addition, mothers of controls had significantly higher maximum systolic blood pressures and maximum diastolic blood pressures during pregnancy than mothers of LBW unexplained antepartum stillbirths (Table 2).

**Table 3.** Odds ratios, 95% CI and $P$-values for normal birthweight unexplained antepartum stillbirths compared with controls, Western Australia 1980–1983: prelabour rupture of membranes and evidence of fetal distress.

| Variable | Odds ratio | (95% CI) | $P$-value |
|---|---|---|---|
| Prelabour rupture of membranes | 0·25 | (0·07–0·90) | 0·034 |
| Evidence of fetal distress* | 3·65 | (1·36–9·80) | 0·010 |

* Defined as recorded in the medical notes, usually meconium stained amniotic fluid or abnormal cardiotocography.

## Discussion

The principal purpose of this study was to investigate details of pregnancies which had resulted in unexplained antepartum stillbirths in an effort to obtain clues as to why these fetal deaths should occur. When compared with matched controls, pregnancies ending in unexplained antepartum stillbirth were less likely to have had medical and pregnancy problems, had less hypertension and anti-hypertensive therapy, and greater weight gain. The relatively large number of stillbirths in women with apparently normal pregnancies indicate that our current clinical and diagnostic systems fail to detect many fetuses at risk of death. The results reflect either incomplete application to the whole population of our clinical laboratory testing systems, or fetal disease states which at present remain undetected by our clinical and laboratory tests. Discovery of new preventable risk factors for unexplained antepartum stillbirths or innovations in the development and application of clinical and laboratory aspects of obstetric care will be required if the rate of fetal deaths currently classified as unexplained is to decrease.

The post mortem rate for unexplained antepartum stillbirths in this study was 70·1% A higher post mortem rate may have decreased the proportion of unexplained stillbirths and the value and importance of fetal and perinatal autopsies in relation to establishing the cause of death needs to be stressed. However, it is recognised that with antepartum stillbirths maceration makes the performance and interpretation of a post mortem difficult.

Few researchers have investigated unexplained antepartum stillbirths as a distinct and separate group of deaths and, to our knowledge, none have compared these stillbirths with a group of liveborn controls matched for birthweight. A number of known risk factors for stillbirth are thought to be associated with, and mediated through, LBW. The inclusion of a group of birthweight matched controls adjusted not only for the effect of birthweight but also for other risk factors associated with this variable. Thus, specific differences between those infants who died *in utero* and those with similar birthweights who survived could be examined. In the literature, the only study found in which matched controls had been used, investigated perinatal mortality in non-malformed babies of 2·5 kg and over. These controls were matched only for place of birth and, although antepartum deaths of unknown cause were identified as a distinct group, they were not analysed separately (Kirkup & Welch 1990).

There are methodological difficulties in studying antepartum stillbirths as death may have occurred several weeks before birth and there were inherent problems in matching on weight at birth. The intention in matching was to obtain a livebirth of similar 'growth' to the stillbirth and, ideally, it would have been best to match for gestational age. However, because the recording of gestational age on midwives' notifications (the data source used for control selection) can be inaccurate, we elected to match for birthweight instead. Accurate information concerning the fetus at the time of death is rarely or cannot be recorded. For example, there may be considerable loss in fetal weight from death *in utero* to birth so that weight at birth is an underestimate of the 'true' fetal weight at death. In addition, gestational age at birth may be an overestimate of the 'actual' gestational age at death. Antepartum stillbirths may therefore falsely appear growth retarded. Control selection in a study of unexplained antepartum stillbirth is an important issue fraught with problems to which there is no clear solution.

The most evident finding of the study was that pregnancy and medical problems (including hypertension) were far more common in mothers of matched controls than in mothers of unexplained antepartum stillbirths. It therefore appeared that pregnancy and medical complications were protective for this type of stillbirth. However, the study design could have led to this result as complicated pregnancies resulting in stillbirths would have been coded on the death certificate as due to the complication and thus not unexplained. Also because these pregnancy and medical risk factors were identified, mothers of controls may have had better surveillance with birth occurring before the infant died *in utero*. Another possibility is that cases were less likely than controls to have pregnancy complications diagnosed because they received less antenatal care. However, there was no evidence of this with there being no difference between cases and controls for the number of antenatal visits (controlling for gestation) and the time of gestation at first visit.

A large proportion of the unexplained antepartum stillbirths were of LBW (54·6%) making this an important factor in the unexplained antepartum stillbirth/control comparision (the controls being matched for birthweight). It appeared from the results obtained for the total population that there may be two different sequences of events leading to LBW and/or preterm birth in unexplained antepartum stillbirths and the matched controls (see Fig. 1). For unexplained antepartum stillbirths it seems that fetal death itself may have been the reason for the LBW and/or preterm birth whereas for the matched controls it was most likely due to the pregnancy and medical complications observed. The analyses of the dichotomized groups investigated this hypothesis further. The results obtained from the LBW group were very similar to those observed in the total population with controls having many more pregnancy and medical complications than unexplained antepartum stillbirths with LBW. In sharp contrast the normal birthweight group displayed very few differences between controls and unexplained antepartum stillbirths with normal birthweight. These results for the dichotomized groups support the above theory of there being two different sequences of events leading to LBW and/or preterm birth in unexplained antepartum stillbirths and controls because the excess of pregnancy and medical complications in controls compared with cases was only observed in the

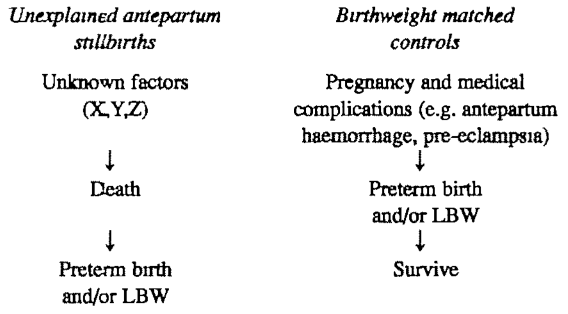
*Unexplained antepartum stillbirths*
*Birthweight matched controls*
Unknown factors (X,Y,Z)
Pregnancy and medical complications (e.g. antepartum haemorrhage, pre-eclampsia)
Death
Preterm birth and/or LBW
Preterm birth and/or LBW
Survive

**Fig. 1.** The hypothesized sequences of events leading to preterm birth and/or low birthweight (LBW) in unexplained antepartum stillbirths and birthweight matched controls.

LBW and not the normal birthweight group. The sequence of events resulting in unexplained antepartum stillbirths over 2500 g has not been clarified by this analysis. However, a better response to evidence of fetal distress may decrease the risk for these normal birthweight stillbirths.

Two pregnancy complications which were more common in mothers of unexplained antepartum stillbirths compared with mothers of controls were polyhydramnios and cord 'abnormalities' (e.g. twisting, spiralling). Polyhydramnios is often associated with lethal and major congenital malformations (Beischer & Mackay 1976; Townsend 1978; Phelan & Martin 1989) but such malformations were excluded from the unexplained antepartum stillbirth group. It may be that polyhydramnios was a marker for some genetic defect which remained undetected. Further research into this finding may provide some clues for unexplained antepartum stillbirth. One way would be to grow cells from all unexplained antepartum stillbirths for karyotyping and DNA analysis, although this is known to be difficult because of the low success rate for cell culture from macerated stillbirths (Jacobs 1990).

The results obtained for cord abnormalities may be explained in terms of observation bias with medical staff being more likely to observe and record a cord abnormality when a baby is stillborn than when it is liveborn. However, if an unbiased observation, it may also suggest an undiagnosed or unrecognized lethal malformation.

Other than polyhdramnios and cord abnormalities, the pregnancy and medical factors analysed in this study have provided no clues as to the aetiology of unexplained antepartum stillbirths. It would seem then that when stillbirths are classified as 'unexplained', they are truly unexplained and that, at present, enquiry into the recorded antenatal antecedents of these stillbirths fails to reveal any further explanation. Thus, other areas need to be considered with respect to determining possible 'causes' of these stillbirths. These possible 'causes' could include fetal factors which as yet cannot be recorded or measured, or maternal factors such as smoking, or the many environmental factors such as diet and occupational hazards. Another possibility is that there may be a proportion of stillbirths that occur because of adverse early pregnancy events, such as genetic and placentation factors.

However, it may be that the most likely scenario is a multifactorial one in which a number of different factors, although individually not fatal, act together to cause the death of the fetus. Continued research into the causes of unexplained antepartum stillbirths may unravel the complex pathway to fetal death and is vital if these stillbirths are to be prevented in the future.

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## APPENDIX

### Numbers for variables analysed in Table 1

| Variable | Unexplained antepartum stillbirths | Matched controls | |
|---|---|---|---|
| | (*n* = 174) | 1 (*n* = 174) | 2 (*n* = 170) |
| Past history | 9 | 15 | 15 |
| ⩾1 previous miscarriage | 26 | 38 | 36 |
| ⩾1 'other' maternal medical disorders | 11 | 28 | 21 |
| Bleeding <20 weeks | 4 | 24 | 17 |
| Bleeding ⩾20 weeks | 9 | 28 | 25 |
| Prelabour rupture of membranes | 7 | 41 | 25 |
| ⩾3 'other' problems in pregnancy | 3 | 19 | 18 |
| Prolonged rupture of membranes | 1 | 11 | 6 |
| Urinary tract infection | 8 | 15 | 12 |
| Cervical sutures and/or threatened preterm labour | 1 | 11 | 11 |
| Placental bleeding | 3 | 11 | 8 |
| Evidence of fetal distress | 16 | 11 | 20 |
| Pre-eclampsia | 10 | 21 | 22 |
| Polyhydramnios | 12 | 0 | 3 |
| Cord abnormalities | 7 | 0 | 2 |
| Average weekly maternal weight gain ⩾0·8 kg/week | 9 | 4 | 2 |
| Antihypertensive therapy | 2 | 13 | 17 |
| Mean arterial pressure in 2nd trimester ⩾90 mmHg | 26 | 19 | 26 |
| Mean arterial pressure in 3rd trimester ⩾90 mmHg | 50 | 42 | 60 |
| Rise in blood pressure from 1st antenatal visit | 47 | 54 | 58 |
| Maximum systolic blood pressure ⩾150 mmHg | 18 | 25 | 36 |
| Maximum diastolic blood pressure ⩾ 100 mmHg | 9 | 22 | 27 |
| Reliable blood pressure data | 114 | 115 | 114 |

### Numbers for variables analysed in Table 2

| Variable | Unexplained antepartum stillbirths | Matched controls | |
|---|---|---|---|
| | (*n* = 95) | 1 (*n* = 95) | 2 (*n* = 92) |
| ⩾1 'other' maternal medical disorders | 7 | 19 | 16 |
| Bleeding <20 weeks | 1 | 19 | 13 |
| Bleeding ⩾20 weeks | 6 | 25 | 23 |
| Prelabour rupture of membranes | 4 | 28 | 18 |
| ⩾3 'other' problems in pregnancy | 1 | 13 | 17 |
| Prolonged rupture of membranes | 1 | 11 | 6 |
| Placental bleeding | 1 | 10 | 7 |
| Evidence of fetal distress | 4 | 9 | 15 |
| Pre-eclampsia | 4 | 19 | 17 |
| Polyhydramnios | 10 | 0 | 3 |
| Antihypertensive therapy | 1 | 13 | 14 |
| Maximum systolic blood pressure ⩾150 mmHg | 9 | 16 | 23 |
| Maximum diastolic blood pressure ⩾100 mmHg | 4 | 17 | 19 |

### Numbers for variables analysed in Table 3

| Variable | Unexplained antepartum stillbirths | Matched controls | |
|---|---|---|---|
| | (*n* = 79) | 1 (*n* = 79) | 2 (*n* = 78) |
| Prelabour of membranes | 3 | 13 | 7 |
| Evidence of fetal distress | 12 | 2 | 5 |

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# A case-control study of intrapartum stillbirths

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**ABSTRACT**

**Objective** To determine antenatal and intrapartum risk factors for intrapartum stillbirths in a total population.

**Design** Matched case-control study.

**Setting** Western Australia 1980–1983.

**Subjects** Intrapartum stillbirths of ≥1000 g birthweight (cases) and liveborn infants (controls) individually matched for year of birth, plurality, sex and birthweight of infant and race of mother.

**Results** Intrapartum stillbirths were more likely than controls to have had placental abruption (OR = 9·55, CI = 2·09–43·69), fetal distress (OR = 4·64, CI = 1·92–11·19), cord prolapse (OR = 10·00, CI = 1·17–85·60) and unhealthy placentas (OR = 2·26, CI = 1·13–4·52), and more likely to have been born by vaginal breech manoeuvre (OR = 3·51, CI = 1·40–8·80) and emergency caesarean section (OR = 2·15, CI = 1·13–4·10); mothers of intrapartum stillbirths were less likely to have had no labour (OR = 0·14, CI = 0·04–0·55) and to have been delivered normally (OR = 0·20, CI = 0·10–0·40). Mothers of cases born by emergency caesarean section had longer labours than mothers of controls born by this method. All intrapartum stillbirths with breech presentation were born by vaginal breech manoeuvre compared with only 53% of the controls; the remainder of the controls were born by caesarean section.

**Conclusions** Results indicate that little could have been done early in pregnancy to prevent the intrapartum stillbirths as no antenatal risk factors predicted these deaths. Most of the risk factors identified related to labour and delivery problems. Considering cases born by emergency caesarean section, delivery of the mother earlier in labour may have prevented some of the deaths.

Intrapartum stillbirths are thought to be the most preventable component of perinatal mortality (Kiely *et al.* 1985; Cruikshank & Linyear 1987; Magani *et al.* 1990). Developing countries still have a high rate of these deaths (Bartlett & Paz de Bocaletti 1991) while in developed countries an intrapartum stillbirth is now an uncommon pregnancy outcome (Lofgren & Polberger 1983; Erkkola *et al.* 1984; Kiely *et al.* 1985; Stanley & Waddell 1985; Albers & Savitz 1991). The dramatic decline in the intrapartum stillbirth rate in developed countries has been noted in a number of descriptive studies (Wood & Renou 1977; Erkkola *et al.* 1984; Stanley & Waddell 1985; Georgsdottir *et al.* 1989) and has been attributed to an improvement in obstetric surveillance and management during labour and the introduction of modern obstetric techniques such as electronic fetal monitoring (Wood & Renou 1977; Shepherd *et al.* 1983; Erkkola *et al.* 1984; Kiely *et al.* 1985; Georgsdottir *et al.* 1989).

There are few studies which have concentrated solely on the ascertainment of risk factors for intrapartum stillbirths using a case-control methodology. Studies have been concerned mainly with the effect of the level of obstetric care on rates of intrapartum fetal death (Kiely *et al.* 1985; Albers & Savitz 1991).

In this paper, and the previous one (Alessandri *et al.* 1992), we describe our investigations of a total cohort of stillbirths in the Western Australian population. Within this cohort we have studied the different types of stillbirth, both antepartum and intrapartum, in an attempt to determine risk factors for each type. This paper presents the results of a matched case-control study investigating antenatal and intrapartum risk factors for the intrapartum stillbirths in the total Western Australian population.

## Subjects and methods

All intrapartum stillbirths weighing 1000 g or more born in Western Australia from 1980 to 1983 inclusive were ascertained from perinatal death certificates collected by the Registrar-General. Definitions and methods have been described in the previous paper (Alessandri *et al.* 1992) with the following additions. Labour and delivery details were obtained from the Midwives' Notification System. In this study, method of delivery was defined as in the Midwives' Notification System; breech manoeuvre includes assisted breech delivery and

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breech extraction (Gee 1990). For those stillbirths who had presented by the breech, the labour and delivery records were scrutinized in an attempt to ascertain the time of intrapartum death and the time of birth. When checking against the Western Australian Congenital Malformations Register (Bower & Stanley 1983), there were two additional intrapartum stillbirths with lethal malformations which had not been identified from the death certificates, and which had originally been classified as cause of death unknown.

In terms of control selection, there were eight cases for whom suitable birthweight matches could not be found in the appropriate year of birth so that one first control and eight second controls were not matched on the year of birth variable. Four of these controls were obtained from the birth year 1979 and the other five were mismatches within the range of the study years of birth. When checking midwives' data with hospital records there were a few discrepancies for birthweight, race and sex. As these were matching variables, these discrepancies led to the exclusion of two controls so that two cases had one control instead of two.

*Analysis*

The analysis for this paper involved comparing intrapartum stillbirths with their birthweight matched controls for the variables of interest using conditional logistic regression. Those stillbirths with lethal congenital malformations together with their corresponding controls were excluded from the study population because these stillbirths were considered unable to be prevented. The data were analysed by means of the Egret software package (Epixact, version 0·02, 1985–1989, Serc & Cytel). For all analyses the results are given in terms of individual odds ratios (OR), their 95% confidence intervals (CI) and $P$-values. A $P$-value of $<0{\cdot}05$ was regarded as being of statistical significance and only significant results were tabulated. The odds ratio approximated the ratio of the proportion of intrapartum stillbirths with the specified variable to the proportion of birthweight matched controls with that variable. Therefore, odds ratios below 1 indicated that the variable was present less often in intrapartum stillbirths than in birthweight matched controls compared with the nominated baseline; odds ratios above 1 indicated it was present more often in intrapartum stillbirths and thus may be a risk factor for this outcome.

**Table 1.** Cause of death for intrapartum stillbirths ≥1000 g; Western Australia 1980–1983.

| Cause of death | *n* | % of all intrapartum stillbirths |
|---|---|---|
| Lethal congenital malformations | 33 | 30·0 |
| Unknown* | 33 | 30·0 |
| Maternal conditions of pregnancy | 2 | 1·8 |
| Maternal hypertension without antepartum haemorrhage (APH) | 5 | 4·5 |
| APH without hypertension | 15 | 13·6 |
| Hypertension with APH | 3 | 2·7 |
| Cord conditions | 6 | 5·5 |
| Hydrops fetalis | 2 | 1·8 |
| Infections | 5 | 4·5 |
| Obstetric trauma | 4 | 3·6 |
| Other (includes maternal trauma, ruptured uterus) | 2 | 1·8 |
| Total | 110 | 99·8 |

* Eight of these had meconium stained amniotic fluid (with or without fetal heart rate abnormalities) recorded; this may be regarded as indicative of fetal distress/intrapartum asphyxia.

## Results

The study population comprised 110 intrapartum stillbirths (cases) and 218 matched controls. The numbers and percentages for each stillbirth cause of death category are shown in Table 1. The most frequent causes of death for intrapartum stillbirths were lethal congenital malformations (30%) and unknown (30%). After excluding the stillbirths with lethal malformations, there were 77 intrapartum stillbirths and 153 matched controls available for analysis.

*Matched case-control analysis*

A number of different groups of variables were investigated. These included: social (father's occupation, mother's conjugal status, maternal height); demographic (maternal age, parity and area of residence); antenatal care (weeks gestation at first antenatal visit, number of antenatal visits, level of hospital of delivery); pregnancy and medical (adverse obstetric history, bleeding at ≥20 weeks, hypertension, prelabour rupture of membranes); fetal and placental (small-for-gestational age infant, macroscopic appearance of placenta); and labour and

**Table 2.** Frequencies for variable categories which were significantly different between intrapartum stillbirths* and controls; Western Australia 1980–1983.

| Variable | Intrapartum stillbirths (*n* = 77) | Matched controls 1 (*n* = 77) | Matched controls 2 (*n* = 76) |
|---|---|---|---|
| Pregnancy problems† | 28 | 19 | 17 |
| Bleeding ≥20 weeks | 18 | 6 | 5 |
| Placental abruption‡ | 10 | 1 | 1 |
| Labour problems§ | 45 | 26 | 25 |
| Fetal distress | 37 | 5 | 8 |
| Cord prolapse | 5 | 1 | 0 |
| Length of labour (h) | | | |
| 0 | 3 | 10 | 10 |
| 1–5 | 31 | 36 | 39 |
| Normal delivery | 19 | 45 | 43 |
| Breech manoeuvre | 14 | 6 | 3 |
| Emergency caesarean section | 22 | 12 | 10 |
| Unhealthy placenta | 35 | 24 | 32 |

* Excludes those with lethal malformations.

† Included conditions such as urinary tract infections, viral or other infections, threatened preterm labour, placental abruption, hyperemesis.

‡ Defined as bleeding from a normally situated placenta causing detachment after 20 weeks gestation and confirmed by retroplacental clot.

§ Included problems such as manual removal of placenta, shoulder dystocia, cephalo-pelvic disproportion, fetal distress, cord prolapse.

**Table 3.** Logistic regression analysis comparing intrapartum stillbirths* with matched controls; odds ratios; 95% CI† and *P*-values for significant variables; Western Australia 1980–1983.

| Variable | Odds ratio | 95% CI† | *P*-value | Baseline |
|---|---|---|---|---|
| Pregnancy problems‡ | 1·91 | 1·02–3·56 | 0·043 | No pregnancy problems |
| Bleeding ≥20 weeks | 4·17 | 1·69–10·81 | 0·003 | No bleeding at ≥20 weeks |
| Placental abruption§ | 9·55 | 2·09–43·69 | 0·004 | No placental abruption |
| Labour problems¶ | 3·12 | 1·70–5·72 | <0·001 | No labour problems |
| Fetal distress | 4·64 | 1·92–11·19 | <0·001 | No fetal distress |
| Cord prolapse | 10·00 | 1·17–85·60 | 0·036 | No prolapsed cord |
| Length of labour (h) | | | | |
| 0 | 0·14 | 0·04–0·55 | 0·005 | 6–12 h of labour |
| 1–5 | 0·43 | 0·22–0·85 | 0·015 | 6–12 h of labour |
| Normal delivery | 0·20 | 0·10–0·40 | <0·001 | No normal delivery |
| Breech manoeuvre | 3·51 | 1·40–8·80 | 0·007 | No breech manoeuvre |
| Emergency caesarean section | 2·15 | 1·13–4·10 | 0·020 | No emergency caesarean section |
| Unhealthy placenta | 2·26 | 1·13–4·52 | 0·021 | Healthy placenta |

* Excludes those with lethal malformations.

† CI = Confidence interval.

‡ Included conditions such as urinary tract infections, viral or other infections, threatened preterm labour, placental abruption, hyperemesis.

§ Defind as bleeding from a normally situated placenta causing detachment after 20 weeks gestation and confirmed by retroplacental clot.

¶ Included problems such as manual removal of placenta, shoulder dystocia, cephalo-pelvic disproportion, fetal distress, cord prolapse.

delivery variables (presentation of infant, onset of labour, type of delivery).

There were no statistically significant differences between cases and controls for any social, demographic or antenatal care variables analysed. Some pregnancy and medical, labour and delivery, and fetal and placental variables did show significant differences; frequencies for these variables for cases and controls are shown in Table 2. Maternal age, parity, adverse obstetric history and level of hospital of delivery were analysed, but there were no significant changes in the odds ratios (maternal age OR = 1·04, CI = 0·98–1·09; parity OR = 0·96, CI = 0·77–1·20; adverse obstetric history OR = 1·25, CI = 0·65–2·41; hospital level of delivery Level 1 compared with Level 3 OR = 1·79, CI = 0·86–3·70).

The pregnancy and medical variables which showed significant differences between mothers of intrapartum stillbirths and those of matched controls were bleeding at ≥20 weeks, pregnancy problems considered as a group (including conditions such as urinary tract infections, viral or other infections, placental abruption, threatened preterm labour and hyperemesis) and placental abruption alone. In logistic regression analyses, these variables were all significantly more frequent in mothers of intrapartum stillbirths than those of controls (Table 3). With respect to fetal and placental variables, significantly more mothers of intrapartum stillbirths than those of controls had unhealthy placentas (including calcification, infarction, anomalies, retroplacental clots) (Table 3).

**Table 4.** Intrapartum stillbirths* and controls, Western Australia 1980–1983: hours of labour by method of caesarean section.

| Method of caesarean section | Hours of labour | | | | |
|---|---|---|---|---|---|
| | 0 | 1–5 | 6–12 | 13 or more | Total |
| (a) Intrapartum stillbirths (total $n$ = 77) | | | | | |
| Emergency | 2 | 8 | 11 | 1 | 22 |
| Elective | 1 | 0 | 0 | 0 | 1 |
| (b) Birth weight matched control groups 1 and 2 (total $n$ = 153) | | | | | |
| Emergency | 10 | 7 | 2 | 3 | 22 |
| Elective | 10 | 0 | 0 | 0 | 10 |

* Excludes those with lethal malformations.

There were many significant differences between mothers of intrapartum stillbirths and those of controls for labour and delivery variables. Mothers of intrapartum stillbirths were significantly more likely to have had labour problems considered as a group (such as manual removal of placenta, shoulder dystocia, cephalo-pelvic disproportion, fetal distress and cord prolapse) than mothers of controls (Table 3). Significantly more intrapartum stillbirths than controls also had fetal distress and cord prolapse when these variables were considered as individual factors (Table 3), but cephalo-pelvic disproportion was not significantly different (OR = 0·55, CI = 0·14–2·19).

In terms of hours of labour, significantly more mothers of controls than mothers of intrapartum stillbirths had labours of 0 and also of 1–5 h (Table 3). Compared with mothers of intrapartum stillbirths, mothers of controls had significantly more normal deliveries. In accordance with this result, mothers of intrapartum stillbirths had significantly more vaginal breech manoeuvres and emergency caesarean sections than mothers of controls (Table 3), but there was no significant difference for elective caesarean section. Further investigations of the data showed that 1 of 77 (1%) of the case mothers had an elective caesarean section compared with 10 of 153 (7%) of the control mothers (Table 4). Also case mothers delivered by emergency caesarean section had longer labours than control mothers delivered by the same method (Table 4).

Although there were no significant differences between cases and controls for breech presentation (18% compared with 11%, $P$ = 0·151) mothers of intrapartum stillbirths had significantly more vaginal breech manoeuvre deliveries than mothers of controls; because of this, we decided to examine frequencies of delivery type by presentation. Of the intrapartum stillbirths who had presented by the breech, 14 of 14 (100%) were delivered by vaginal breech manoeuvre whilst 9 of 17 (53%) of the controls with breech presentation were vaginal breech deliveries; the remaining 8 of the controls (47%) were delivered by caesarean section (3 elective and 5 emergency). Detailed examination of the labour and delivery records showed that for 11 of 14 stillbirths who had presented by the breech, the fetal heart beat was still present when the decision was made to proceed with a vaginal delivery. The labour and delivery records could not be found for the remaining three stillbirths with breech presentations.

## Discussion

The aim of this study was to determine risk factors for intrapartum stillbirths in a total population. Compared with matched controls, intrapartum stillbirths were more likely to have had placental abruption, fetal distress, cord prolapse, unhealthy placentas and to have been born by vaginal breech manoeuvre and emergency caesarean section. Intrapartum stillbirths were less likely to have had short labours and normal births. There were no significant differences between intrapartum stillbirths and their matched controls for the maternal social, demographic and antenatal care variables investigated.

Although mothers of intrapartum stillbirths were at increased risk from bleeding at ≥20 gestation, in the majority of cases this bleeding occurred close to the time of birth, being associated with placental abruption. Therefore, obstetric intervention may have had little effect in preventing these intrapartum fetal deaths. Where there was an interval of some weeks between the bleeding and the time of birth, it may have been possible to prevent the infant being stillborn by earlier birth. However, this decision is always difficult because of the problem of extreme immaturity of the infant if born too early. The association of intrapartum fetal death with pregnancy problems was due mainly to placental abruption and other antepartum haemorrhage. Other pregnancy problems also contributed to the increased risk but the numbers for these problems were too small to analyse them separately. The excess of unhealthy placentas in mothers of cases may have been due to biased recording as, in a retrospective study of this type, the placenta is likely to have been more closely examined after the birth of a stillborn infant than after a livebirth. This may also have been the situation with some other variables which were not recorded before the infant was born.

Not surprisingly, there were significantly more labour problems in mothers of intrapartum stillbirths than in those of controls. The increased risk associated with labour problems was mostly because of the association with fetal distress and, to a lesser extent, cord prolapse with other problems contributing in a minor way. In terms of hours of labour, control mothers were more likely to have had shorter labours than case mothers. This could be explained by mothers of controls having had more deliveries by elective and emergency caesarean sections. Mothers of intrapartum stillbirths, however, had significantly more emergency caesarean sections than mothers of controls but case mothers were more likely to have been delivered by caesarean section after long labours. Conversely, the control mothers were more likely to have had emergency sections after short labours. Perhaps birth by emergency section earlier in labour could have prevented some of the intrapartum stillbirths in the study. Cruikshank *et al.* (1987) found that the major cause of intrapartum fetal death (among term infants weighing at least 2500 g without congenital malformations) was long delay between the onset of obvious fetal compromise and birth.

There were marked differences between cases and controls with respect to delivery type. Controls were more likely to have been born normally while cases were more likely to have been born by vaginal breech manoeuvre or emergency caesarean section. Amongst the 77 cases, there was only one elective caesarean section (1%), whereas there were 10 amongst the 153 controls (7%). The results concerning breech presentation and method of birth may imply that the case infants presenting by the breech would have had a better chance of survival if they had been born by section, particularly as at least 11 out of 14 were still alive when a decision was made on mode of delivery.

In contrast to other studies, no significant results were obtained for parity, adverse obstetric history and level of hospital of delivery. Studies have shown primiparity to be a significant risk factor for intrapartum stillbirths (Kiely *et al.* 1986; Barlett & Paz de Bocaletti 1991) with one study also showing a strong relation between high parity and intrapartum fetal deaths (Kiely *et al.* 1986). Prior fetal loss, which was included in our combined variable of adverse obstetric history, has been noted by others as being associated with intrapartum fetal death (Kiely *et al.* 1985; 1986).

Studies have also shown that the level of obstetric or perinatal care available in the hospital of delivery is strongly related to intrapartum stillbirth (Kiely *et al.* 1985; Albers & Savitz 1991). In these previous studies intrapartum death rates increased as the level of hospital of delivery decreased. An explanation for not obtaining significant results for the three above mentioned variables in our study could be because cases and controls were closely matched on birthweight. The associations found in previous studies may have been confounded through inadequate control of birthweight (Kiely 1991b). The studies concerning level of hospital of delivery did make some attempt to control for birthweight but this was not done stringently, with one study adjusting for ≤2500 g and >2500 g birthweight (Albers & Savitz 1991) and the other adjusting for birthweight in 500 g intervals (Kiely *et al.* 1985). It is important to note that, in agreement with our results, there has been one published study which has shown no significant differences between level of hospital of delivery and fetal death during labour (Bakketeig *et al.* 1978). However, another study which investigated the quality of obstetric care for each individual mother and infant did find an association between suboptimal obstetric care and fetal death: antepartum and intrapartum deaths were considered together but there were only 5 intrapartum deaths out of a total of 58 stillbirths (Niswander *et al.* 1984).

There is a need for prospective studies on intrapartum stillbirths to enable better and more detailed data collection and there is some evidence that the findings from randomised controlled trials would be implemented by obstetricians, at least with regard to the preterm breech infant (Penn & Steer 1991). However, the numbers of intrapartum stillbirths in developed countries are too small for prospective studies to be completed in a reasonable time span. In our study, there were no antenatal risk factors that could have predicted an intrapartum stillbirth so it appears that little could have been done early in pregnancy to avoid these deaths. Most of the risk factors pertained to labour and delivery problems and there were important associations with method of delivery. For births presenting by the breech, elective or emergency caesarean section may have prevented some of the deaths. This retrospective study was designed to generate hypotheses regarding the outcome of stillbirth and not specifically to investigate breech presentation and, in a few cases, we have been unable to delineate the precise sequence of events. However, in the absence of a well designed randomised controlled trial, or a prospective study, we can only be guided by results from retrospective studies. Our work supports Kiely *et al* (1991a) who have found that the outcome for infants presenting by the breech is more favourable if they are born by caesarean section rather than vaginally.

Data pertaining to the use of electronic fetal monitoring during labour were not collected for this study but, as the stillbirths occurred from 1980–1983, it would have been in use for approximately 12% of all births (Stanley & Watson 1988). Further investigations of intrapartum stillbirths in Western Australia for more recent years should be performed, since electronic fetal monitoring is now more widely used in this population.

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OBSTETRICS

# Risks of anal incontinence from subsequent vaginal delivery after a complete obstetric anal sphincter tear

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**ABSTRACT**

**Objective** To assess the influence of various risk factors on long term anal incontinence in women with a complete obstetric tear of the anal sphincter.

**Design** Postal questionnaire.

**Setting** Department of Gynecology and Obstetrics, Aarhus University Hospital, Denmark.

**Subjects** 152 women with complete obstetric tear of the anal sphincter.

**Main outcome measures** Occurrence and duration of anal incontinence in relation to any delivery.

**Results** 56 of 121 respondents had experienced a subsequent vaginal delivery; 23 (41%) of these had had transient anorectal incontinence directly after the complete tear and four (7%) had permanent anorectal incontinence. In the 23 women with transient anorectal incontinence directly after the complete tear, 9 (39%; 95% CI 19%–59%) developed anorectal incontinence after the next delivery, and this was permanent in four (17·4%; 95% CI 2%–33%). In the 29 women without anorectal incontinence after complete tear, two had transient incontinence of flatus but for less than 14 days after the next delivery.

**Conclusions** Transient anal incontinence after a complete tear is a predictor of anal incontinence after subsequent vaginal delivery. The major long term problem in our study of premenopausal women was incontinence of flatus. This possibility should be discussed with the women when a further pregnancy is planned.

Women with complete obstetric tears of the anal sphincter (complete tear) have a high risk of anal incontinence (Haadem *et al.* 1988).

In general women who have had a complete tear are allowed to have a vaginal delivery in subsequent pregnancies. It has been suggested that further vaginal delivery might be associated with increased risk for anorectal incontinence (Laurberg *et al.* 1988), but there has been no study designed to address this question.

We have investigated the long terms effect on anal continence of a complete tear and have assessed the influence of various risk factors.

## Subjects and methods

In the period between 1 January 1976 and 30 October 1987, 41 000 consecutive vaginal deliveries occurred at our clinic; 152 of these women had a complete obstetric tear of the anal sphincter (complete tear). In our clinic all complete tears are confirmed and treated by a senior registrar or a consultant. The ruptured sphincters were all sutured with two or three absorbable sutures. For the first 4 postoperative days the women were not allowed to sit up. Mild laxatives were given until the first defaecation. Pelvic floor exercises were started on the fifth day, and the women were encouraged to continue these after returning home. Prophylactic antibiotics were not used. In our clinic there was no special management policy for the next delivery for women with a previous complete tear.

In 1989 the 152 women were asked to complete a questionnaire concerning the occurrence and duration of anal incontinence in relation to *any* delivery. The questionnaire was completed by 121 women (80%); 28 did not return the questionnaire and five had emigrated.

Fifty six (46%) of the 121 women who had had a complete tear and answered the questionnaire had had a subsequent vaginal delivery. These 56 women are the subject of this report.

We used multiple logistic regression analysis to investigate whether transient anal incontinence occurring after a complete tear was associated with an increased risk of anal incontinence after a subsequent vaginal delivery. A general logit model was achieved using an iterative procedure to obtain maximum likelihood estimates of effects (Breslow & Day 1980). Other factors that might be associated with anal incontinence were represented in the model, including maternal age, birthweight, parity, use of oxytocic agents and instrumental delivery (forceps or vacuum) at the time of the occurrence of the complete tear, and maternal age at the next vaginal delivery. Maternal age and birthweight were dichotomised at 30 years and 4000 g, respectively.

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**Table 1.** Association between anorectal incontinence directly after a complete tear and after the next vaginal delivery in 56 women.

| Degree of anorectal incontinence after next vaginal delivery | Anorectal incontinence directly after a complete tear | | |
|---|---|---|---|
| | None ($n$ = 29) | Transient ($n$ = 23) | Permanent ($n$ = 4) |
| Flatus | 2 | 3 permanent<br>1 unknown | 3 unchanged<br>1 aggravated |
| Faecal soiling | 0 | 1 permanent<br>1 for 3 months<br>1 for 9 months | 0 |
| Complete* | 0 | 2 for 1 month | 0 |
| None | 27 | 14 | 0 |

*Incontinence to solid stools.

**Table 2.** Association between transient anal incontinence directly after a complete tear and anal incontinence after the next vaginal delivery in 52* women.

| Anal incontinence after complete tear | Anal incontinence after next delivery | | | |
|---|---|---|---|---|
| | Yes | No | Odds ratio | $P(\chi^2$ test) |
| Yes | 9 | 14 | 8·7<br>(1·9–39) | 0·005 |
| No | 2 | 27 | | |

*Four women with permanent anal incontinence after complete tear are **not** included.

## Results

### *Anal incontinence after complete tear*

Of the 121 women returning the questionnaire, 50% experienced anal incontinence after complete tear.

Fifty-six (46%) of the 121 women had had a vaginal delivery after the complete tear. Of these 56 women, 27 (48%) developed anal incontinence after the complete tear, and this was transient in 23 women (41%) (Table 1).

### *Anal incontinence after subsequent delivery*

Of the 23 women with transient anal incontinence after complete tear, nine (39%; 95% CI 19%–59%) had anal incontinence after a subsequent delivery. This incontinence was permanent in four (17%; 95% CI 2%–33%). Of the four women with persistent incontinence of flatus after complete tear, one had an increase in incontinence of flatus after her next delivery but the symptoms were unchanged in the other three.

Of the 29 (52%) women without anal incontinence after complete tear, two experienced incontinence of flatus for 14 days after their subsequent delivery (Table 1).

Transient anal incontinence after a complete tear was significantly associated with development of anal incontinence after the next delivery (bivariate analysis: odds ratio 8·7 (95% CI 1·9–39 $P$<0·005) (Table 2).

Logistic regression analysis showed that transient anal incontinence after complete tear was the only factor that increased the risk of anal incontinence after the next delivery. When adjusted for the other factors included in the analysis the odds ratio was 23 (95% CI 3·7–150).

## Discussion

Vaginal delivery can result in damage to the pelvic floor innervation (Snooks *et al.* 1984; 1985; 1986). Some damage seems to persist and this may be cumulative in multipara (Snooks *et al.* 1984; 1986). It has been suggested that women with evidence of nerve damage to the pelvic floor may become incontinent in later life (Snooks *et al.* 1986). Of women with anal incontinence after complete tear, 60% have evidence of pudendal nerve damage (Snooks 1985). The outcome of surgical repair of the sphincter defect is influenced by the coexistence of pudendal nerve damage (Laurberg *et al.* 1988).

Our findings confirm the results of Hadeem *et al.* (1988) that approximately 50% of women who have a complete tear experience anal incontinence. We found that this incontinence was usually transient. However, after the next vaginal delivery 39% of those with transient anal incontinence after complete tear experienced a relapse of anal incontinence; in four (17%) of these women, this anal incontinence was permanent. In women without anal incontinence after a complete tear there was no permanent anal incontinence after the next vaginal delivery although two women (7%) had incontinence of flatus for up to 14 days.

None of the women included in our study had reached the menopause. Since the occurrence of anal incontinence increases after the menopause (Gooszen *et al.* 1987), the frequency of permanent anal incontinence we observed must be considered as a minimum. Women with anal incontinence may not seek medical advice as they are often too ashamed and embarrassed to discuss their problem (Browning & Motson 1983). We therefore recommend that all women with complete tear should be offered clinical assessment at an appropriate interval after delivery.

The major long term problem in our study was incontinence of flatus. This possibility should be discussed with the women when planning the next pregnancy, but further studies are needed to give a more precise estimate of the risk of anorectal incontinence in subsequent deliveries.

## Acknowledgments

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## ERRATUM

# Experience with the Cardial inferior vena cava filter as prophylaxis against pulmonary embolism in pregnant women with extensive deep venous thrombosis

In the article by Dr. H. Narayan and her colleagues featured in the August issue, the x-ray photograph, (Fig. 3 p. 639), illustrating the position of the Cardial filter was printed upside down due to a typographical error at revised proof stage by the printers of this Journal. Apologies are extended to Dr Narayan and her co-authors for this error and the photograph is reprinted below. It is important to stress that the position of the filter in the inferior vena cava is now shown correctly. (Narayan *et al.* 1992, *Br J Obstet Gynaecol* **99**(8), pp. 637–640.)

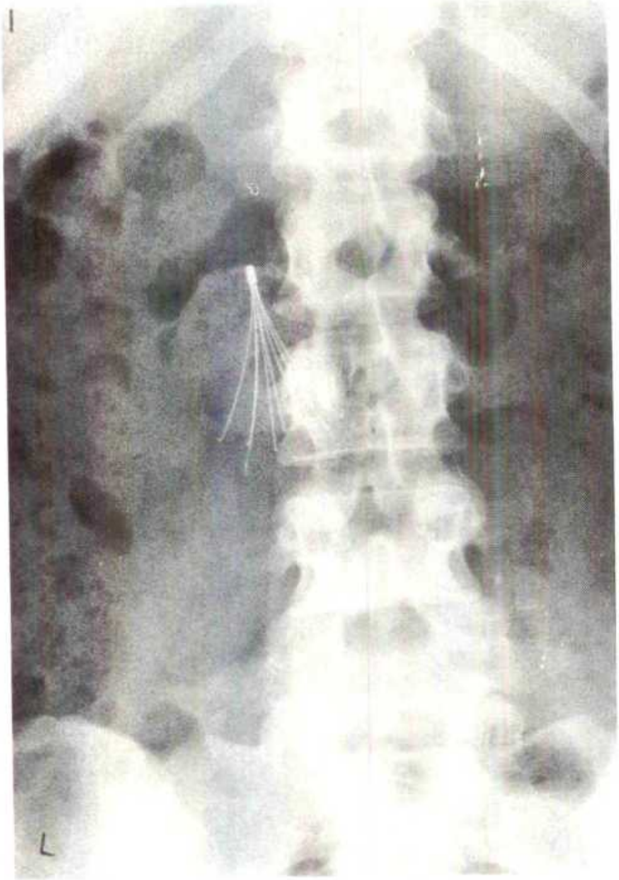

**Fig. 3.** Abdominal X-ray in the puerperium: Filter in correct position in the inferior vena cava.

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OBSTETRICS

# A comparative study of the use of epoprostenol and dihydralazine in severe hypertension in pregnancy

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**ABSTRACT**

**Objective** To compare the antihypertensive effects of epoprostenol sodium (prostacyclin) with that of dihydralazine in acute hypertensive crises of pregnancy.

**Design** A prospective randomized study. A minimum of 20 patients per group was considered statistically acceptable (alpha = 0·05, power = 0·9).

**Setting** A large urban tertiary hospital.

**Subjects** Forty-seven pregnant patients with diastolic blood pressures of >100 mmmHg were studied.

**Intervention** Lowering of high blood pressure with either dihydralazine ($n$ = 25), the standard drug for this purpose, or epoprostenol ($n$ = 22).

**Main outcome measure** A significant drop in high blood pressure was regarded as a fall of 15 mmHg diastolic and 30 mmHg systolic blood pressure.

**Results** There were no statistically significant differences in the antihypertensive effects between the two treatment groups. Epoprostenol infusion caused less tachycardia; the mean pulse rate changed from 81·77 beats/min, before treatment to 88·36 at stabilization, compared with a change from 80·96 beats/min to 102·68 in the group treated with dihydralazine ($P$ = 0·0024).

**Conclusion** The place of epoprostenol in pregnancy might be in patients with severe hypertension and tachycardia and in those requiring acute control of severe hypertension on the operating table before general anaesthesia.

Although the primary cause of pre-eclampsia still eludes researchers in this field, disturbances in prostanoid metabolism, in particular an imbalance in the opposing actions of thromboxane and prostacyclin, have been implicated in its aetiology (Walsh 1985; Downing *et al.* 1982; Moodley *et al.* 1984). This has led to the use of prostacyclin ($PGI_2$) to lower high blood pressure, particularly in acute hypertensive emergencies of pregnancy (Belch *et al.* 1985).

A recent pilot study of the $PGI_2$ (epoprostenol sodium) in 10 primigravid women with severe hypertension showed that prostacyclin was effective in lowering high blood pressure in all patients (Moodley 1990). The present study was performed to compare the antihypertensive effects of prostacyclin with that of dihydralazine, the standard drug for lowering very high blood pressure in hypertensive crises of pregnancy at King Edward VIII Hospital (KEH), Durban.

## Subjects and methods

Ethical permission for the study was obtained from the Faculty of Medicine (UN) Professional Standards and Ethics Committee. Informed, written consent was obtained from 47 patients who presented with severe hypertension in pregnancy to the delivery suite of KEH. King Edward VIII Hospital is a large urban tertiary hospital serving an indigent population. A minimum of 20 patients per group was considered statistically acceptable (alpha = 0·05, power = 0·9). A significant drop in high blood pressure was regarded as a fall of 15 mmHg diastolic and 30 mmHg systolic blood pressure. All patients had diastolic blood pressures of greater than 110 mmHg and at least one plus (+) of proteinuria detected on dipstix (Ames). Only women of more than 33 weeks gestation were included in the study. Excluded from the study were patients who had symptoms of imminent eclampsia or who required immediate delivery for obstetric reasons.

All patients were managed using a standard protocol as described previously by Moodley *et al.* (1983), except for antihypertensive therapy. Initial management included sedation in the form of a barbiturate, gardenal sodium (200 mg intramuscularly), and bed rest. If the high blood pressure did not settle within 2 h, the patients were included in the study.

They were then allocated to one of two groups using random number tables; Group 1 received epoprostenol sodium (prostacyclin) and Group 2 dihydralazine (nepresol). Before infusion of antihypertensive therapy, all patients had a central venous line using a drum catheter (Abbott) through an antecubital vein. If the central venous pressure was low, it was cor-

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rected to a level of 5 cm $H_2O$ with Ringer's lactate solution before lowering of high blood pressure. In addition, a Foley catheter was inserted to record urine output hourly, and the fetal heart rate was recorded continuously with an antepartum fetal heart rate monitor (Hewlett-Packard 101A). Placental abruption was excluded by clinical means by cardiotocographic recording demonstrating normal fetal heart rate patterns and normal uterine activity patterns before antihypertensive therapy. Blood pressure and pulse rate were measured every 5 min in the left lateral position until the blood pressure was lowered to mean arterial pressure of 105 mmHg (MAP = diastolic + ⅓ pulse pressure) and stabilization was achieved. Laboratory investigations included estimation of haemoglobin concentration, packed cell volume and platelet count. In addition, urates, creatinine, urea, electrolytes and fibrinogen levels were measured. Radiography of the chest was performed to confirm placement of the central venous line, and the electrocardiographic recordings were monitored visually.

### *Epoprostenol infusion*

The infusion was given through an infusion pump. The initial rate of infusion of epoprostenol sodium was 0·5 ng/kg/min and was increased to a maximum of 10 ng/kg/min in a stepwise manner until the blood pressure was controlled at a level of 140/90 mmHg or lower. The infusion rate was increased by 1·5 ng/kg/min at 15 min intervals with the object of reaching a maximum infusion of 10 ng/kg/min within 120 min. If the appropriate fall in blood pressure was reached at a particular infusion rate, the infusion was continued at this rate. However, if the diastolic blood pressure fell to 90 mmHg or less, the drip rate was decreased. The prostacyclin infusion was continued for 24 h after delivery.

### *Dihydralazine infusion*

Dihydralazine infusion was given through an infusion pump, beginning at a drip rate of 0·5 mg/kg/min and increasing the rate every 15 min until a maximum of 1·5 mg/kg/min was reached.

Both dihydralazine and epoprostenol infusions were continued for 24 h after delivery following the achievement of a MAP of 105 mmHg at that particular rate. In patients requiring caesarean section, the infusion and all monitoring of the patient was continued during the procedure.

**Table 1.** Clinical and laboratory data in the two treatment groups.

| Variable | Epoprostenol ($n$ = 22) | Dihydralazine ($n$ = 25) |
|---|---|---|
| Age (years) | 21·45 (4·13) | 21·52 (5·04) |
| Weight (kg) | 65·36 (9·54) | 65·44 (11·66) |
| Gestational age (weeks) | 36 (32–40) | 36 (32–40) |
| Primigravida | 16 (72·7%) | 18 (72%) |
| Multigravida | 6 (27·3%) | 7 (29·2%) |
| Haemoglobin (g/dl) | 10·71 (2·66) | 11·09 (1·05) |
| Platelet count /µl | 261·14 (77·58) | 258·8 (131·07) |
| Urates (mmol/l) | 0·38 (0·06) | 0·39 (0·07) |
| Creatinine (mmol/l) | 70·86 (14·12) | 72·16 (16·58) |

Results are reported as means (SD) or $n$ (%) values as appropriate, gestational age is shown as the median (range) values.

### *Statistics*

For continuous data, the Student's $t$-test was used to compare the two treatment groups, adjusting for unequal variances where appropriate. For discrete data, the $\chi^2$ test was used and where the expected cell frequency was less than 5 in the 2 × 2 case, Fisher's exact test was utilized.

## Results

### *Clinical and laboratory data*

The clinical data of all patients is shown in Table 1. Of the 22 women treated with epoprostenol, 16 (73%) were in their first pregnancy compared with 18 of the 25 (72%) women treated with dihydalazine. All patients had proteinuria. In Group 1, 16 patients had proteinuria 2+ or 3+ compared with 10 patients in Group 2. There were no significant differences between the two treatment groups in respect of clinical or laboratory variables.

### *Obstetric and neonatal data*

There were no significant differences between the groups in respect to the method of delivery. Of the 22 women in Group 1, 13 (60%) were delivered by caesarean section, compared with 20 of the 25 (80%) in Group 2. The most common reason for abdominal delivery in both groups was fetal heart rate decelerations: 11 in Group 1 and 14 in Group 2. Failure of normal progression of labour accounted for the remainder. There was one neonatal death in each treatment group. The neonatal death in Group 2 occurred in a 1·3 kg baby born hypothermic, hypoglycaemic, puffy and with skin lesions. Fetal heart rate decelerations had been recorded before unsuccessful attempts to lower the high maternal pressure. In Group 1, the neonatal death occurred on the 5th day following delivery. The baby weighed 1 kg and was severely growth retarded and developed respiratory problems at birth.

### *Cardiovascular data*

Table 3 shows the cardiovascular data in both groups during the study period. All values are the means (SD) of several readings taken at 5 min intervals. There were no significant differences in heart rate, systolic or diastolic blood pressures or central venous pressure between the groups on admission. Difficulty in controlling blood pressure did not occur in any patients receiving epoprostenol. However, in two patients in the dihydralazine group there was failure to reduce blood pressure sufficiently before caesarean section and both demon-

**Table 2.** Obstetric and neonatal outcome in the two treatment groups.

| Variable | Epoprostenol ($n$ = 22) | Dihydralazine ($n$ = 25) |
|---|---|---|
| Birthweight (g) mean (SD) | 2432 (689) | 2160 (512) |
| Neonatal deaths | 1 | 1 |
| Small for gestational age | 10 | 13 |
| Appropriate for gestational age | 12 | 12 |
| Ventilation necessary | 2 | 7 |
| Caesarean section | 13 (60%) | 20 (80%) |

**Table 3.** Cardiovascular data on admission and after treatment in the two treatment groups.

| | On admission | | After treatment | |
|---|---|---|---|---|
| Variable | Epoprostenol | Dihydralazine | Epoprostenol | Dihydralazine |
| Pulse rate/min | 81·77 (14·33) | 80·96 (8·27) | 88·36 (13·23) | 102 68 (17·91) |
| Blood pressure (mmHg) | | | | |
| Systolic | 173·95 (22·33) | 185·04 (27·31) | 150 36 (11·82) | 156·5 (10·26) |
| Diastolic | 116·86 (8·50) | 122·08 (11·95) | 92 59 (10·59) | 93·28 (13·08) |
| Central venous pressure | 7·00 (3·29) | 6·52 (3·10) | 7·32 (3·50) | 6·68 (3·67) |

Results are mean (SD) values.

*The change in pulse rate effected by treatment was significantly different between the two treatment groups, $P = 0{\cdot}0024$.

strated significant decelerations in fetal heart rate, one before and one after treatment. Additional use of a rapidly acting ganglion blocking agent (trimetaphan) before the induction of general anaesthesia was necessary in these patients. After caesarean section their blood pressure decreased to within the normal range. Post delivery blood pressure control was satisfactory in all the women in both groups.

Both groups showed an increase in pulse rate (Table 3) following treatment but there was a significant difference between the groups at stabilization ($P = 0{\cdot}0024$). Systolic and diastolic blood pressures were reduced by treatment in both groups. However, there was no statistically significant difference between the two groups. The time required to achieve this control was significantly less in patients receiving epoprostenol (mean 51·1 SD 37·8 min) than in patients who received dihydralazine (mean 86·8 SD 47·7 min) ($P = 0{\cdot}0072$).

Side effects of treatment were seen in only two patients. Nausea and vomiting occurred in one patient treated with epoprostenol and severe headache occurred in a patient treated with dihydralazine. Both responded to symptomatic treatment.

## Discussion

Amongst the characteristics of an ideal antihypertensive drug for the acute lowering of high blood pressure are that such drugs should have no maternal side effects, lower blood pressure smoothly without resultant hypotension and have no effects on uteroplacental blood flow. Dihydralazine, a potent vasodilator, is probably the most commonly used antihypertensive drug for the acute lowering of high blood pressure in pregnancy despite concern over its effects on uteroplacental blood flow. Vink *et al.* (1980) have reported fetal heart rate decelerations following acute reduction of blood pressure from severely hypertensive to normotensive levels. In practice, however, reduction of severe hypertension to safe levels is seldom accompanied by evidence of distress In some women, usually those with severe intrauterine growth retardation, fetal heart rate changes do occur and identify the women requiring early delivery rather than conservative management.

Dihydralazine is also associated with maternal side effects of nausea, vomiting and reflex tachycardia. Thus, when epoprostenol was found to be effective in lowering high blood pressure in pregnancy and especially because there is a deficiency of $PGI_2$ in pre-eclampsia (Walsh 1985; Downing *et al.* 1982; Moodley *et al.* 1984; Belch *et al.* 1985), it was decided to compare the effects of dihydralazine and epoprostenol in the acute control of severe hypertension in pregnancy. In the present study, epoprostenol was effective in lowering high blood pressure in all patients. Its effects were seen earlier than that of dihydralazine (mean 51·14 SD 37·79 min *vs* mean 86·80 SD 47·72 min; 95% CI) for the difference (10·89 to 60·43). The increase in pulse rate was significantly less than that caused by dihydralazine (Table 3) Dihydralazine was given by infusion in this study; this may have accounted for its delayed action compared with epoprostenol. Dihydralazine by infusion, whilst recommended by some authors (Davey 1972) and used in this study for the purposes of comparison, may not be the ideal method of using the agent because the peak effect of an administered dose may be delayed by 20–30 min. This might account for the delay in achieving the desired decrease in blood pressure in the dihydralazine group and also might be partly responsible for the two treatment failures in that group.

Rebound hypertension associated with epoprostenol infusion (Moodley 1990; Toppozada *et al.* 1987) was not observed in the present study. This was probably due to the fact that the infusion was continued for 24 h after delivery and that the dose was reduced gradually rather than stopped abruptly.

In a study of seven patients with acute pre-eclampsia and six with superimposed pre-eclampsia, Jouppila *et al.* (1985) found no changes in maternal pulse or fetal pulse rate or uterine contractility. Moreover, epoprostenol infusion did not alter placental and fetal blood flow. In the present study all patients had proteinuric hypertension (diastolic blood pressures of ⩾100 mmHg) and they had a mean gestational age of 36 weeks. A large number, however, had fetal heart rate decelerations (11 in Group 1 and 14 in Group 2), during antihypertensive therapy. This is probably due to the fact that fetal growth retardation was a feature in 23 patients (10 in Group 1 and 13 in Group 2) and it is well known that in the presence of severe intrauterine growth retardation, treatment will lead to evidence of fetal distress. Lowering of blood pressure and continuous fetal heart rate monitoring in such circumstances thus acts as fetal stress test cautioning against conservative treatment of pre-eclampsia.

The neonatal death in each group, occurring in small babies, is in keeping with the high risk characteristics of the population studied. The overall perinatal mortality for hypertensive pregnancies at King Edward VIII Hospital is 80 per 1000 deliveries (unpublished data).

Epoprostenol has been reported to result in troublesome flushing, but there was a relative lack of side-effects in the present study. All patients in this study were African and indigenous. This possibly could be due to racial differences.

Overall, as the infusion of epoprostenol is effective in lowering high blood pressure in pre-eclampsia without causing a maternal tachycardia. In the regimen used in this study, it was not associated with rebound hypertension or maternal side effects. Although it is questionable whether its antihypertensive effect has a marked superiority over dihydralazine, it was 100% effective in this study. Many patients with eclampsia and imminent eclampsia have marked tachycardias. Its place, therefore, might be in this group of patients who require acute control of severe hypertension to prevent complications such as cerebral haemorrhage and pulmonary oedema. Furthermore, it may have a role in lowering high blood pressure before general anaethesia as endotracheal intubation causes marked rises in blood pressure.

## Acknowledgments

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OBSTETRICS

# Determinants of pregnancy heartburn

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**ABSTRACT**

**Objective** To study the prevalence and severity of reflux symptoms in pregnancy.
**Design** Self-administered questionnaire detailing age, race, gestational age, parity, weight, height, symptoms and severity of gastro-oesophageal reflux.
**Setting** An antenatal clinic in a teaching hospital.
**Subjects** 607 consecutive women at various stages of pregnancy were recruited during attendance at antenatal clinic.
**Results** The prevalence of heartburn increased with gestational age (22% in the first, 39% in the second, and 72% in the third trimester; $P<0{\cdot}0001$), as did severity of heartburn ($P<0{\cdot}0001$). Pharyngeal regurgitation as a symptom showed little increase during advancing pregnancy. Symptoms of heartburn rapidly increased towards the end of the second trimester. The decrease in heartburn traditionally expected during the last three weeks of pregnancy (fetal head descent) was not observed. Logistic regression analysis showed increased risk of suffering heartburn with increasing gestational age ($P<0{\cdot}0001$), pre-pregnancy heartburn ($P<0{\cdot}0001$), parity ($P<0{\cdot}0001$) and inversely with maternal age ($P<0{\cdot}05$) but not with body mass index before pregnancy, race, or weight gain in pregnancy.
**Conclusion** Heartburn, but less so pharyngeal regurgitation, increases in prevalence and severity with gestational age and parity. We speculate that hormone-related impairment of distal oesophageal clearance mechanisms may have a crucial bearing on whether heartburn develops in those individuals at greatest risk.

Heartburn is a common symptom that is estimated to afflict up to two-thirds of pregnant women (Atlay *et al.* 1973). Since the occurrence of this symptom rises with advancing gestation (Atlay *et al.* 1973; Feeney, 1982), increasing intra-abdominal pressure, resulting from expansion of the uterus, has traditionally been advanced as the explanation (Feeney 1982). Alternatively, it has been proposed that hormonal changes in pregnancy result in changes in gut motor function which, among other effects, lead to abnormal gastro-oesophageal reflux. In this respect, studies in small numbers of women during and after pregnancy (Van Thiel *et al.* 1977), women taking sequential oral contraceptives (Van Thiel *et al.* 1976) and animal models (Schulze & Christensen 1977) have suggested that sex hormones reduce lower oesophageal sphincter pressure and thereby impair its function as a barrier to gastro-oesophageal reflux. This hormonal theory is supported largely by circumstantial evidence and has never been proven directly (Dodds *et al.* 1978), but it is clear from studies in patients with ascites (Van Thiel & Wald, 1981) that raised intra-abdominal pressure alone is an inadequate explanation for gastro-oesophageal reflux in pregnancy.

Concepts of pathogenesis of gastro-oesophageal reflux disease have advanced considerably (de Caestecker & Heading 1989) since the period over 10 years ago when most research into pregnancy heartburn was undertaken. Low basal lower oesophageal sphincter pressure is no longer thought to be the main mechanism permitting reflux to occur in gastro-oesophageal reflux disease, and the condition appears to be complex and multifactorial in its aetiology. Our aim was to study the epidemiology of pregnancy heartburn in order to determine its prevalence, severity and time of onset and to determine whether any predisposing factors could be identified. The findings are set in the context of recent advances in understanding of gastro-oesophageal reflux disease.

## Subjects and methods

A total of 607 women attending antenatal clinic at St. George's Hospital were given a detailed self-administered questionnaire about heartburn and pharyngeal regurgitation. Terminology was clearly defined in lay terms in the questionnaire. Heartburn was defined as 'a burning sensation or discomfort behind the breastbone that often extends upwards to the throat' and pharyngeal regurgitation as 'clear fluid reaching the mouth or throat and causing a bitter or acidic taste'. Women were asked about these symptoms during and before pregnancy, and to rate their symptoms (if any) over the previous 7 days on a scale of severity and frequency as shown in Table 1. An overall score was derived from the product of scores for severity and frequency. Parity, date of last menstrual period, age, ethnic origin, height and weight (both before pregnancy and at the time of

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Table 1. Grading system for severity and frequency of oesophageal symptoms.

| Symptoms | Definition | Score |
|---|---|---|
| Severity | | |
| None | No symptoms | 0 |
| Mild | Not interfering with daily activities | 1 |
| Moderate | Interfering with daily activities | 2 |
| Severe | Constant, severely disrupting activities | 3 |
| Frequency | | |
| Rarely | Less than once a week | 1 |
| Often | 2 or more times a week | 2 |

Severity and frequency independently scored for day and night over previous 7 days. Overall score of severity = (frequency × severity score for day) + (frequency × severity score for night)

administration of the questionnaire) were recorded for each patient. Body mass index was calculated as weight (in kg) divided by the square of the height ($m^2$). We obtained from published data values for changes in fundal height (Calvert *et al.* 1982), plasma progesterone (Johansson 1969) and oestriol excretion (Klopper & Billewicz 1963), during normal pregnancy. These data were chosen because a complete set of results for each week of pregnancy was provided.

### *Statistics*

Results are expressed as mean (SE) unless otherwise indicated. Frequency and severity of heartburn or pharyngeal regurgitation during different stages of pregnancy were compared by analysis of variance (ANOVA), Kendall $\gamma$ coefficient of correlation or $\chi^2$ test as appropriate. Logistic regression analysis was used to unravel and rank the effects of different variables on the presence of heartburn; those women in whom details of gestational age or race were not provided (see below) were excluded from this analysis.

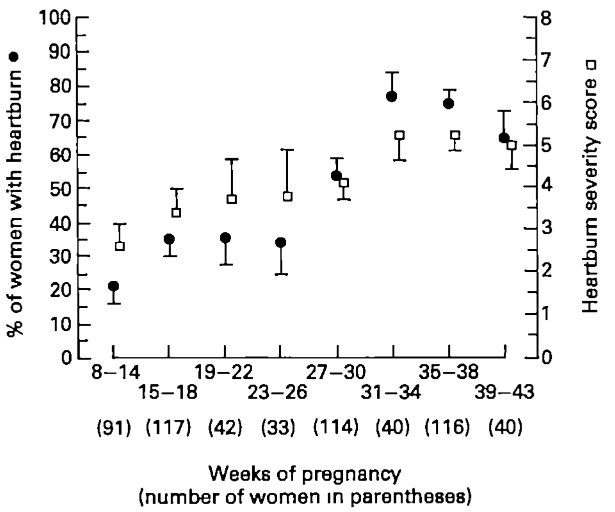

Fig. 1. Prevalence and severity of heartburn (mean and SE) plotted against gestational age. Gestational age represented as 4-week periods (except first period of 8–14 weeks, which spans a longer period).

## Results

### *Demographic data*

The results of the 607 questionnaires are included in the analyses that follow. However, there were some incomplete questionnaires as detailed below.

The mean (SD) age of the antenatal clinic responders was 29·5 (6·4) years. Ninety-one were in the first trimester of pregnancy, 274 in the second and 228 in the third trimester (14 did not provide details of gestational age). There were 394 Caucasians, 98 Asians and 85 Afro Caribbeans (no details of race in 31). Two hundred and twenty-six were primigravid, 177 were in their second pregnancy and 204 were in at least their third pregnancy.

### *Questionnaire*

The prevalence of heartburn increased significantly from 22% (20 of 91 women) through 39% (106 of 274 women) to 72% (164 of 228 women) in the first, second and third trimesters, respectively ($\chi^2 = 85{\cdot}8$, $P<0{\cdot}0001$). Mild heartburn (as defined in Table 1) was reported in 14% (82 of 607 women) of individuals before pregnancy. The pattern of prevalence and severity of heartburn during pregnancy showed a progressive increase through pregnancy (Fig. 1) with a particularly marked increase at the end of the second trimester (Kendall $\gamma = 0{\cdot}25$, $P<0{\cdot}0005$ for prevalence and $\gamma = 0{\cdot}29$, $P<0{\cdot}0001$ for severity).

Pharyngeal regurgitation showed a small increase in prevalence with advancing pregnancy (Kendall $\gamma = 0{\cdot}14$, $P<0{\cdot}0001$) but not severity (Kendall $\gamma = -0{\cdot}08$, NS; Fig. 2). The prevalance and severity of both heartburn and pharyngeal regurgitation were not significantly different in weeks 39–43 compared with the preceding 4-week period. The pattern of increase of heartburn is closely paralleled by changes in urinary pregnanediol, but the changes in fundal height and urinary oestriol levels appear to follow a different time pattern (Fig. 3).

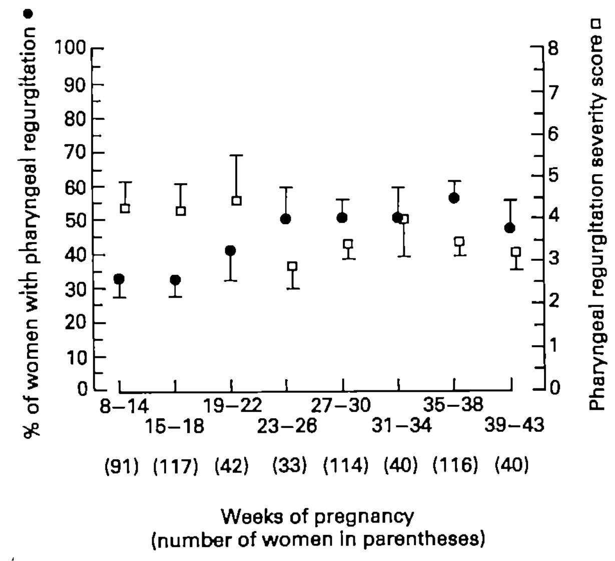

Fig. 2. Prevalence and severity of pharyngeal regurgitation plotted against gestational age. Results displayed as for Fig. 1.

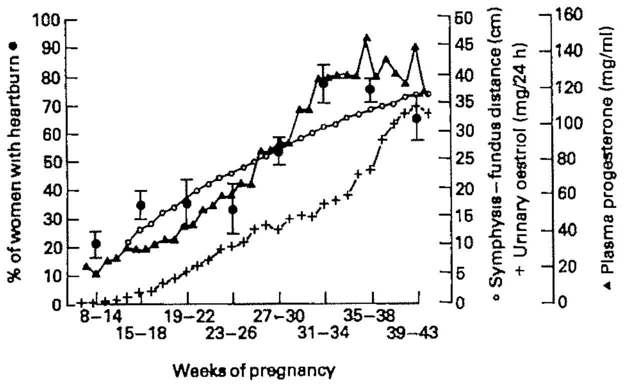

**Fig. 3.** Time pattern of prevalence of heartburn, symphysis-fundus height, plasma progesterone and urinary oestriol excretion with gestational age. Values for heartburn prevalence are mean and SE for 4-week periods. The other values are taken from published data (Johansson 1969; Klopper & Billewicz 1963; Calvert *et al.* 1982) as detailed in the text. These data are all mean values plotted against gestational age at weekly intervals, in order to graphically display the pattern of change.

The overall frequency of heartburn in pregnancy showed no difference by race (50%, 45% and 50% for Caucasians, Afro-Caribbeans and Asians, respectively). Since it has already been established that the prevalence of pregnancy heartburn increases with gestational age, one possibility that needs to be excluded is that the lack of difference in frequency of heartburn observed in this study between ethnic groups is not the result of a sampling bias. The mean gestational ages at the time of administration of the questionnaire were similar (mean (SE) 26·1 (0·5), 25·5, (1·0) and 23·5 (1·0) weeks for Caucasians, AfroCaribbeans and Asians, respectively). Although these values are not significantly different between Caucasians and AfroCaribbeans, mean gestational age was significantly shorter in Asians compared with Caucasians ($P<0{\cdot}05$, ANOVA). This finding, while not ruling out a small selection bias for Asian women, is at least compatible with the conclusion that the ethnic groups examined do not suffer less pregnancy heartburn than Caucasians.

Gestational age, heartburn before pregnancy and parity were identified as significant predictors of suffering pregnancy heartburn by logistic regression analysis (Table 2). Maternal age showed a weak inverse correlation with heartburn. Gestational age showed the strongest association with heartburn (Table 2). Race, body mass index before pregnancy and weight gain in pregnancy were not found to be risk factors for pregnancy heartburn.

## Discussion

The prevalence of pregnancy heartburn found in this study is similar to that reported previously (Atlay *et al.* 1973; Feeney 1982; Nagler & Spiro 1961). Like Atlay *et al.* (1973) we were unable to confirm suggestions (Bassey 1977) that pregnancy heartburn is rare in ethnic Africans, and indeed found no evidence that race is a significant risk factor for pregnancy heartburn, nor any difference in risk between ethnic groups. Reduction in heartburn has been claimed following fetal head descent immediately before term (Rodway & Shelley 1935) and this observation has been used to support a mechanical explanation for pregnancy heartburn. However, we were also unable to support this view. The reason for the association of higher parity with heartburn is unclear, but is unlikely to be the result of increasing age, since this showed only a weak inverse correlation with the occurrence of heartburn.

The most important factor to emerge as a predictor of heartburn was gestational age. When this was considered, weight gain was not found to be an independent predictor of heartburn in its own right. This being so, it is no surprise to find that the pattern of rise of plasma progesterone more closely mirrors changing prevalence and severity of heartburn with advancing pregnancy than fundal height (Fig. 3). This would tend to support the view that a hormonal effect on lower oesophageal function is a more important determinant of the develpoment of heartburn than any mechanical effect of raised intra-abdominal pressure.

Progesterone is known to be essential for the maintenance of pregnancy in all mammals. Its action, however, is complex but it maintains the myometrium in a quiescent state (Turnbull 1989). A side effect of this may be generalized smooth muscle relaxation and inspection of Fig. 3 suggests a close temporal relation between heartburn prevalence and plasma progesterone. No such relation is seen with urinary oestriol secretion.

An important effect of rapidly rising gestational hormones is clearly to impair oesophageal smooth muscle function so that the lower oesophageal sphincter barrier function is impaired. However, another important effect could be on reducing effective oesophageal clearance of refluxed gastric contents through impairment of distal oesophageal peristalsis. It was interesting that there was no increase in the severity of pharyngeal regurgitation through pregnancy, and the frequency of this symptom showed a less marked increase than did heartburn. If it is assumed that the frequency of regurgitation is proportional to the number of episodes of gastro-oesophageal reflux actually occurring, it would appear that these increase only modestly. It could therefore be speculated that impaired oesophageal clearance rather than impaired lower oesophageal sphincter function is a more important factor in the third trimester of pregnancy.

Can our findings be interpreted in the light of current concepts of gastro-oesophageal reflux disease (de Caestecker & Heading 1989)? Firstly, low basal lower oesophageal sphincter pressure, once thought to be the most important determinant of gastro-oesophageal reflux both in pregnancy (Nagler & Spiro 1961; Lind *et al.* 1968) and in other situations (Cohen & Harris 1971), is now known not to be the main factor permitting reflux to occur. Rather, reflux occurs during intermittent transient episodes of lower eosophageal sphincter relaxation (Dent *et al.* 1988). It is not known whether pregnancy affects this mechanism, but since it appears that these transient relaxations are under vagal control (de Caestecker & Heading 1989), it would seem unlikely that this would be affected by the hormonal and intra-abdominal pressure changes occurring in pregnancy. Secondly, oesophageal clearance of refluxed gastric contents has been shown to be an important determinant of how long after a reflux episode has occurred gastric contents remain in contact with the oesophageal mucosa (de Caestecker & Heading 1989; Stanciu & Bennett 1974). Not all episodes of reflux are associated with heartburn, but there is evidence that heartburn is more likely to occur with longer lasting periods of con-

**Table 2.** Logistic regression analysis of the effect of seven variables on the presence of pregnancy heartburn.

| Variable | γ | Coefficient (95% CI) | Probability |
|---|---|---|---|
| Gestational age | 8·67 | 0·102 (0·078, 0·126) | <0·0001 |
| Heartburn before pregnancy | 5·28 | 1·84 (1·04, 2·54) | <0·0001 |
| Parity | 4·05 | 0·309 (0·157, 0·461) | <0·0001 |
| Maternal age | −2·31 | −0.045 (−0·006. −0·084) | <0·05 |
| Weight gain during pregnancy* | −1·13 | −0·029 (−0·081, 0·022) | NS |
| Body mass index before pregnancy | 0·89 | 0·026 (−0·022. 0·084) | NS |
| Race | −† | −† | NS |

*Weight at stage of administration of questionnaire compared to pre-pregnancy weight.
†Values not given, as 2 'dummy' variables used in logistic regression analysis.

tact of the oesophageal mucosa with refluxed gastric contents (Lacey Smith *et al.* 1989). Furthermore, it appears that oesphageal sensory receptors may be sensitized by long lasting episodes of acid gastro-oesophageal reflux so that subsequent reflux episodes are more likely to be symptomatic (Lacey Smith *et al.* 1989). If oesophageal clearance mechanisms in particular are disturbed during the period of rapid rise in gestational hormones in the third trimester of pregnancy, this may be an important factor in the increased frequency and severity of heartburn during this period. The relative contributions of impaired lower oesophageal sphincter function, delayed oesophageal clearance and increased oesophageal sensitivity during pregnancy merit further detailed study.

Our data suggest that women of high parity and with the symptom of heartburn before pregnancy are at increased risk of developing pregnancy heartburn. If the hypothesis advanced above is correct, perhaps these individuals should be advised to adopt the very measures currently advocated to treat gastro-oesophageal reflux (e.g. nocturnal bed elevation) at an early stage before heartburn is a major problem, in an effort to prevent oesophageal sensitization and severe reflux symptoms.

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FETAL AND NEONATAL MEDICINE

# Do fetal pulse oximetry readings at delivery correlate with cord blood oxygenation and acidaemia?

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## ABSTRACT

**Objective** To assess the accuracy of a pulse oximeter in the fetus.
**Design** A prospective descriptive study, comparing oxygenation and acidaemia of cord blood with oxygen saturation in the arteries of the fetal scalp measured by a pulse oximeter just before delivery. The data were collected using an experimental pulse oximeter and a sensor specifically adapted to cope with the problems of fetal pulse oximetry.
**Setting** The labour ward in a teaching hospital.
**Subjects** Thirty seven Caucasian fetuses presenting by the vertex in normal uncomplicated labour.
**Main outcome measure** Fetal pulse oximetry reading shortly before birth, umbilical cord oxygenation and pH, and Apgar scores.
**Results** Data of sufficient quality were obtained from 28 fetuses. There was a highly significant correlation between pulse oximetry reading and umbilical vein oxygen saturation $r = 0{\cdot}59$, $P = <0{\cdot}001$). There was also a significant correlation between the pulse oximeter reading and cord blood pH (vein: $r = 0{\cdot}57$, $P = 0{\cdot}002$, artery: $r = 0{\cdot}63$, $P = 0{\cdot}001$). Apgar scores were not related to the oximetry results.
**Conclusion** Pulse oximetry readings reflect fetal oxygenation at birth.

Pulse oximetry is a non-invasive technique that has been used extensively by anaesthetists and neonatologists to monitor arterial oxygen saturation continuously. It is a logical progression to use this intensive care technology in labour to identify the fetus at risk. Adult and neonatal sensors are not suitable for monitoring the fetus as they use light transmitted through tissue and it is not possible to transmit this light through the fetal head. We have developed a sensor that works on the principle of reflectance pulse spectrophotometry (Fig. 1). We have further modified the oximeter to amplify the fetal signal, increase the signal to noise ratio and discriminate the fetal signal from artifact. The equipment was calibrated using pregnant sheep hystereotomy models (Jongsma *et al.* 1991). To assess the accuracy of this prototype fetal pulse oximeter in the human fetus, we performed a prospective validation study by comparing oximetry readings at birth with cord blood measurements.

## Subjects and methods

We recruited 37 women in uncomplicated labour with a singleton pregnancy and a vertex presentation. These included women who were scheduled for artificial rupture of the membranes and women whose membranes had ruptured spontaneously.

We used a newly designed fetal oximetry sensor and an experimental pulse oximeter (Nellcor Inc., California, USA) specifically adapted for fetal application. The power to the light emitting diodes originates from a microprocessor in the pulse oximetry box. The photodetector signal is passed through a preamplifier and signal filters to be stored on a Toshiba T5100 lap top computer. Here, the computer program assesses the signal quality using multiple parameters including signal amplitude, consistency, purity and synchronicity with the R wave of the fetal ECG collected from a Copeland electrode. The quality of each pulse signal is analysed by combining scores awarded for each parameter. The pulse is compared to a standard plethysmograph and the quality described as a fraction of a perfect signal. Data are accepted only if (i) the signal quality is greater than 60% of the theoretical perfect pulse; (ii) both plethysmographs colours are synchronous; (iii) they

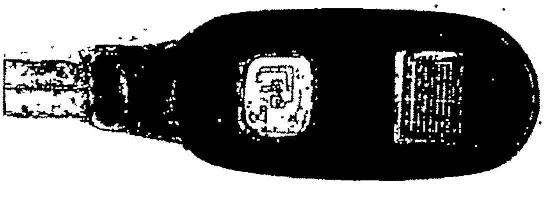

**Fig. 1.** Fetal pulse oximetry sensor. (2 5 cm long; 1·1 cm wide; 0 3 mm deep, light source to centre of detector distance = 9·5 mm).

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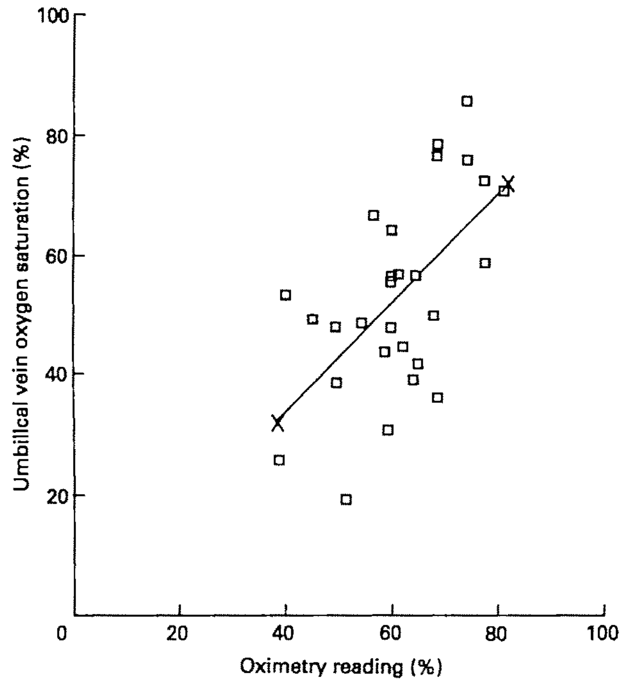

Fig. 2. The relation between the fetal pulse oximetry reading in the second stage of labour and umbilical cord venous oxygen saturation

have the typical appearance of a fetal signal; (iv) they coincide with the QRS complex of the fetal ECG; and (v) if they have a high and consistent pulse amplitude. The fetal oximetry sensor was disinfected in a solution of 2% glutaraldehyde for 20 min before placement. After consent had been obtained, a vaginal examination was performed at the next routine assessment. The fetal sensor was placed between the cervix/lower uterine segment and the fetal head and its position was adjusted until the pulse signal was satisfactory. The fetus was monitored up to and during birth. At birth, the timing of the following events was recorded: crowning, birth of the head, sensor removal, birth of the body, clamping of the cord and drawing of the cord blood samples. At birth the cord was double clamped and samples of artery and vein cord blood were obtained anaerobically using heparinised 2 ml syringes. The samples were analysed without delay in an ABL3000 blood gas analyser (Radiometer, Copenhagen) (Paerregaard *et al.* 1987). Data from poor samples (e.g. samples with air bubbles or duplicated measurements differing by 10%) were discarded.

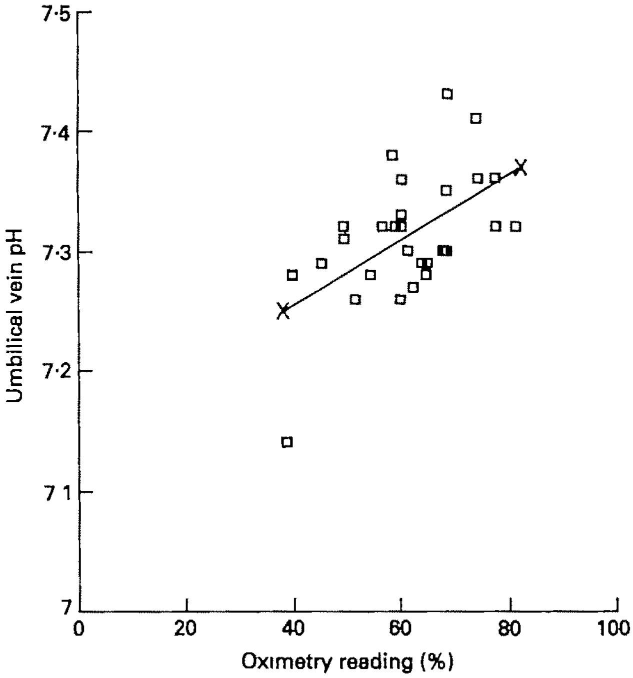

Fig. 3. The relation between the fetal pulse oximetry reading in the second stage of labour and umbilical cord venous pH.

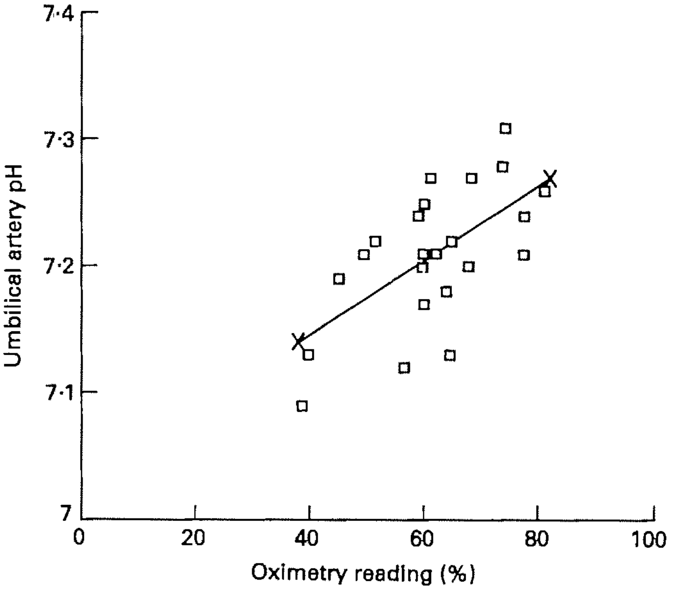

Fig. 4. The relation between the fetal pulse oximetry reading in the second stage of labour and umbilical cord arterial pH.

Data from each fetus were examined in detail. We looked at the recorded oximetry signal in each fetus and noted the time between the birth of the trunk and the most recent section of acceptable signal. We analysed the data only where an acceptable signal had been obtained within the last 30 min before the birth of the trunk. Linear regression analysis and Pearson's correlation coefficients were used to correlate the average oxygen saturation with umbil-

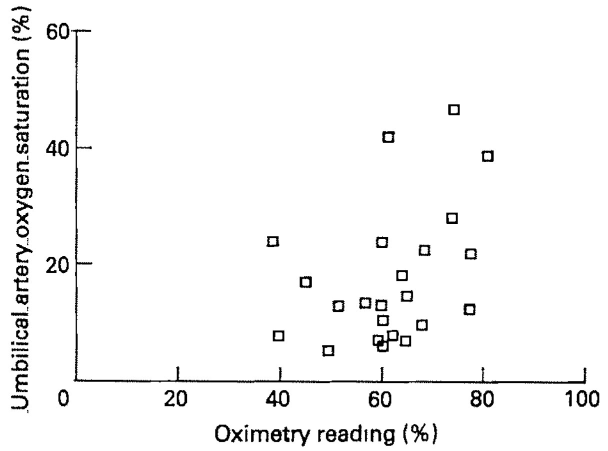

Fig. 5. The relation between the fetal pulse oximetry reading in the second stage of labour and umbilical cord arterial oxygen saturation.

**Table 1.** The correlation of mean pulse oximetry reading in the second stage of labour.

| Outcome variable | Number of readings | *r* value | *P* value |
|---|---|---|---|
| Umbilical vein $O_2$ saturation | 28 | 0·59 | <0·001 |
| Umbilical artery $O_2$ saturation | 23 | 0·39 | 0·57 |
| Umbilical vein pH | 28 | 0·56 | 0·002 |
| Umbilical artery pH | 28 | 0·63 | 0·001 |
| Vein-artery pH difference | 23 | −0·043 | 0·84 |
| Apgar score at | | | |
| 1 min | 28 | 0·15 | 0·45 |
| 5 min | 28 | −0·074 | 0·71 |

**Table 2.** The correlation of pulse oximetry reading for fetusers with valid signal occurring within 10 min of birth.

| Outcome variable | Number of readings | *r* value | *P* value |
|---|---|---|---|
| Umbilical vein $O_2$ saturation | 20 | 0·57 | 0·009 |
| Umbilical artery $O_2$ saturation | 15 | 0·58 | 0·023 |
| Umbilical vein pH | 20 | 0·50 | 0·025 |
| Umbilical artery pH | 15 | 0·66 | 0·007 |
| Vein-artery pH difference | | No improvement | |
| Apgar score at | | | |
| 1 min | | No improvement | |
| 5 min | | No improvement | |

ical vein and artery blood oxygen saturation, vein and artery pH, venous-arterial pH difference and Apgar scores.

## Results

Of the 37 fetuses with stored raw oximetry signals within 30 min of birth, nine were rejected because the data quality did not meet the criteria for acceptability. In the remaining 28, there was a statistically significant correlation between the oximetry reading and umbilical vein (fetal oxygenation blood) oxygen saturation, umbilical vein pH and umbilical artery (fetal deoxygenated blood) pH (Figs 2–4). There was no statistically significant correlation between the pulse oximeter result and umbilical artery oxygen saturation (Fig. 5) or the difference between vein and artery pH ($pH_{(vein)}-pH_{(artery)}$). The Pearson's correlation coefficients comparing oximetry readings with 1 min and 5 min Apgar scores are 0·15 ($P$ = 0·45) and −0·74 ($P$ = 0·71), respectively (Table 1).

If the analysis was restricted to include only fetuses whose most recent oximetry signal occurred within 10 min of birth ($n$ = 20), the correlation between the oximetry reading and umbilical artery oxygen saturation became significant (Fig. 6). Restricting the analysis did not improve the correlation between the oximetry reading and Apgar scores (Table 2).

## Discussion

Previous work studying the accuracy of fetal pulse oximetry using a Criticare 502 oximeter showed no correlation between pulse oximeter oxygen saturation and either umbilical vein or artery oxygen saturation ($r$ = 0·04; $P$ = 0·81 and 0·03; $P$ = 0·84, respectively). This equipment had not been adapted for fetal use, the sensor components were inadequate and the signal processing could not discriminate motion artifact from a pulse (Johnson *et al.* 1991). Furthermore, commercial pulse oximetry equipment is designed to monitor adults and newborn infants using transmitted light. Such equipment is not able to process the smaller signal caused by lower perfusion pressures and small vascular beds from the fetus and the monitors are not calibrated below saturations of 70%. Thus commercial equipment, even if equipped with reflectance sensors, is unsuitable for fetal use. Our data collection system was designed to cope with all of the problems of a small fetal signal, interference, noise, reflectance sensors, low levels of saturation, intrauterine use and fetal apposition.

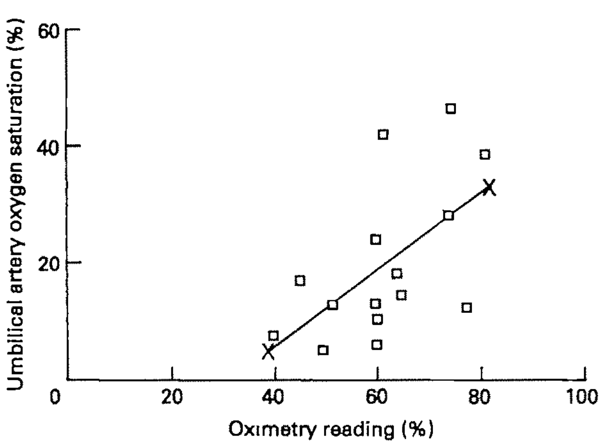

**Fig. 6.** The relation between the average fetal pulse oximetry reading 10 min before delivery and umbilical cord arterial oxygen saturation.

In this series there was a highly significant correlation between the oxygen saturation in the arteries of the fetal scalp (pulse oximetry reading) and umbilical vein oxygen saturation when all 28 fetuses with acceptable quality data were included. The correlation between pulse oximetry reading and umbilical artery oxygen saturation only became significant when the analysis was restricted to data obtained within 10 min before delivery. This suggests that umbilical artery oxygen saturation (fetal blood returning to placenta) changes more rapidly from moment to moment than umbilical vein oxygen saturation ('oxygenated' blood from the placenta). The poor correlation between oximetry reading and Apgar scores is no surprise as the latter are poor predictors of oxygenation at delivery.

This is the first study to demonstrate that pulse oximetry readings can reflect fetal oxygenation at birth in the human. Previous reports have demonstrated that a reduction in oxygen saturation pre-empts CTG changes (Johnson & Johnson 1989; Johnson 1991; Rooth 1987; McNamara & Johnson 1992) and that the use of fetal pulse oximetry will increase the specificity of the cardiotocograph (Peat *et al.* 1988; Johnson & Lilford 1988; Gardosi *et al* 1989; McNamara *et al.* 1992). Our pulse oximeter has been specially modified for fetal use and is capable of measuring fetal oxygen saturation. The effect of monitoring fetal oxygenation on clinical outcome is less certain but we now have a tool which will help us to assess this fundamental question.

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FETAL AND NEONATAL MEDICINE

# The role of abnormal fetal heart rate in scheduling chorionic villus sampling

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**ABSTRACT**

**Objective** To assess the value of fetal heart rate (FHR) measurements in predicting spontaneous fetal loss in pregnancies scheduled for chorionic villus sampling (CVS).

**Design** A prospective descriptive study.

**Setting** Two hospital departments of obstetrics and gynaecology in Israel.

**Subjects** 114 women between 9 and 11 weeks gestation scheduled for chorionic villus sampling (CVS).

**Interventions** Fetal heart rate was measured by transvaginal Doppler ultrasound and compared with a monogram established from 75 fetuses. Whenever a normal FHR was recorded, CVS was performed immediately.

**Results** 106 women had a normal FHR and underwent CVS; two of these pregnancies ended in miscarriage. In five pregnancies no fetal heart beats could be identified and fetal death was diagnosed. In three pregnancies an abnormal FHR was recorded and CVS was postponed; all three pregnancies ended in miscarriage within 2 weeks.

**Conclusion** Determination of FHR correlated with crown-rump length could be useful in predicting spontaneous miscarriage before performing any invasive procedure late in the first trimester.

Chorion villus sampling (CVS) for prenatal genetic diagnosis is believed to incur a higher risk of fetal loss than midtrimester amniocentesis. To obtain an accurate estimate of the incidence of CVS related fetal loss, instances of spontaneous miscarriage must be discounted. This is especially true because CVS is generally performed late in the first trimester, when miscarriage is not uncommon. Moreover, the rate of miscarriage is related to maternal age, and is greater than 10% in women aged 40 years and over (Achiron & Tadmor 1991), which is precisely the population most frequently referred for prenatal genetic diagnosis. Thus, it is urgent to define prognostic criteria for spontaneous miscarriage in women scheduled for CVS.

It has been shown recently that fetal bradycardia and fetal tachycardia are associated with a high rate of miscarriage (Cohen-Overbeek *et al.* 1990). In that study, a very good correlation was demonstrated between fetal crown rump length (CRL) and fetal heart rate (FHR), which proved to be better than the correlation between FHR and gestational age.

The aim of the present study was to investigate the prognostic potential of fetal heart rate in pregnancies scheduled for CVS.

## Subjects and methods

Our study group consisted of 114 women scheduled for transcervical CVS between 9 and 11 weeks gestation. Indications for CVS were as follows: maternal age >35 years (74 women); a previous pregnancy with chromosomal abnormalities (13 women); fetal cystic hygroma (six women); a chromosomal translocation in the woman or her partner (10 women) and possible hereditary disorders for which diagnosis by DNA analysis is available (11 women). Gestational age was determined from the onset of the last menstrual period and corroborated by crown rump length (CRL).

Sonographic studies (6.5 MHz ESI 1000, Elscint Israel) included measurements of the mean gestational sac diameter and the longest CRL. Using a transvaginal approach, the yolk sac could be easily distinguished from the embryonic pole, leading to more accurate measurement. The embryonic heart rate was obtained from the Doppler spectrum using electronic calipers so the average time interval (in ms) between five consecutive beats was measured. Sixty divided by this number provided the number of heart beats per minute. Duration of Doppler investigation in each patient was approximately 2 min. A 200 Hz high-pass filter was used to remove signals from slow-moving tissues in the path of the Doppler beam. Ultrasonographic energy was maintained at 100 mW/cm$^2$ spatial peak temporal average intensity, well below the known peak acoustic field emission of 180 mW/cm$^2$ for pre-enactment ultrasonographic diagnostic devices. An earlier study showed a good correlation between CRL and FHR (Achiron & Tadmor 1991).

To establish the normal range of FHR, a nomogram for FHR

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and CRL was established for fetuses between 9 and 11 weeks gestation. Altogether, 75 fetuses were scanned as described above, 25 for each week. The average maternal age of this group was 39.1 years which is the average age of women scheduled for CVS in our institution. This study group was confined to women with regular menstruation, with a reliable date of their last period and with no history of bleeding in the current pregnancy. These pregnancies were followed until the end of the second trimester and only three of them ended in fetal death. Determination of embryonic viability and gestational age were the indications for early routine scan. All women gave their informed consent. All scans were performed by a single observer.

In our prenatal diagnosis group, CVS was performed immediately after ultrasonographic assessment whenever normal FHR was recorded. However, when an abnormal FHR (2 SD from the mean) was identified, CVS was postponed, subject to re-assessment.

## Results

Mean values for FHR and upper and lower limits as a function of CRL of the 75 fetuses of the control group, are summarized in Table 1. The results of this group are almost identical to our results in an earlier study (Achiron & Tadmor 1991).

In the series of 114 women scheduled for CVS, 106 had normal FHR and they were sampled immediately. Of these 106 pregnancies with normal FHR, two ended in miscarriage. In five pregnancies, no fetal heart beats could be identified at the initial scan and fetal death was diagnosed. In three pregnancies the recorded FHR was abnormal: one was a woman referred for CVS for the diagnosis of Tay-Sachs disease at 9 weeks gestation. The CRL of the fetus was compatible with gestational age, but significant and persistent bradycardia (> 2SD below the mean) was identified. A week later, a miscarriage was clearly seen. In the other two pregnancies, CVS was recommended for fetal karyotyping because of the maternal age of 40 years. The exact gestational ages were unknown at the times scheduled for CVS. Relative fetal tachycardia (> 2SD above the mean) was diagnosed in both pregnancies and CVS was delayed. A week later fetal death was identified.

**Table 1.** Fetal heart rates as a function of crown rump length (CRL) (Mean ±SD).

| | Fetal heart rate (beats/min) | | | | |
|---|---|---|---|---|---|
| CRL (mm) | −2SD | −1SD | Mean | +1SD | +2SD |
| 17–18 | 155 | 163 | 170 | 177 | 183 |
| 19–20 | 159 | 165 | 171 | 176 | 181 |
| 21–22 | 151 | 162 | 172 | 181 | 190 |
| 23–24 | 151 | 161 | 172 | 181 | 189 |
| 25–26 | 162 | 167 | 173 | 179 | 185 |
| 27–28 | 158 | 165 | 172 | 179 | 186 |
| 29–30 | 164 | 169 | 174 | 180 | 187 |
| 33–34 | 157 | 166 | 175 | 183 | 190 |
| 35–36 | 159 | 166 | 174 | 182 | 191 |

In four of the 106 pregnancies investigated with CVS, abnormal karyotypes were found. Three fetuses had trisomy 21 and one found to have 45 × 46 xY mosaicism in the CVS sample had a normal 46 xY karyotype at amniocentesis. All these features had normal FHR recordings.

## Discussion

This study demonstrates the role of abnormal FHR in predicting spontaneous fetal loss in pregnancies scheduled for CVS. A first trimester fetal loss rate of 1·8% was recorded in the group subjected to CVS (2 of 106 pregnancies). Had CVS been performed without regard to FHR, a fetal loss rate of 4·6% (5/109) could have been recorded and erroneously related to the CVS procedure.

Thus we recommend that FHR be measured and correlated with CRL before performing any invasive procedure in the first trimester, such as CVS, selective fetal reduction, or early amniocentesis. This should assist in predicting a miscarriage, which will no longer be ascribed erroneously to procedure-related pregnancy loss.

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FETAL AND NEONATAL MEDICINE

# Fetal heart rate in early pregnancy and chromosomal disorders

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## ABSTRACT

**Objective** To investigate normal fetal heart rate in early pregnancy and assess the hypothesis that abnormal fetal heart rate is associated with fetal chromosomal abnormalities.

**Design** Prospective descriptive cross-sectional study.

**Setting** Antenatal clinic associated to the University Clinic of Obstetrics, University Hospital Groningen, The Netherlands.

**Subjects** 424 pregnant women who attended for prenatal counselling.

**Interventions** Measurements of fetal heart rate from 6–16 weeks gestation, cross-sectional study.

**Main outcome measures** Fetal heart rate expressed as beats/min.

**Results** Karyotyping showed a normal chromosomal pattern in 414 fetuses. The median fetal heart rate increased from 138 beats/min at 6 weeks to 177 beats/min at 9 weeks, thereafter, fetal heart rate gradually decreased to 150 beats/min at 16 weeks. Karyotyping showed 10 abnormalities: five trisomies 21, three trisomies 18, and two mosaic patterns in chorionic villi. Fetal heart rate of the trisomic fetuses was distributed around the median with that of all Down's syndrome fetuses within the normal range. In one fetus with trisomy 18, the heart rate exceeded the 90th centile, in another it fell under the 10th centile. The two fetuses with a mosaic pattern in chorionic villi had heart rates outside the normal range.

**Conclusion** Fetal heart rate in chromosomally abnormal fetuses in early pregnancy do not appear to be consistently different from that in normal fetuses. The use of a single measurement of fetal heart rate is not valuable for screening purposes. Chromosomal mosaicism in chorionic villi may be associated with abnormal fetal heart rate.

Fetal cardiac activity can be detected from approximately 40 days postmenstrual age onwards (Cadkin & McAlpin 1984; Schats *et al.* 1990a; Cacciatore *et al.* 1990). Heart rate is initially low, increases to a peak value of about 170 beats/min at 9 weeks and gradually decreases thereafter (Robinson & Shaw-Dunn 1973).

In the pregnancies followed longitudinally that ended in an early miscarriage low fetal heart rates have been found and some of the fetuses have been chromosomally abnormal (Laboda *et al.* 1989; Schats *et al.* 1990a). In a fetus with Down's syndrome the heart rate was consistently low and it has been suggested that an early abnormal heart rate might be an indication for chorionic villus sampling or amniocentesis (Schats *et al.* 1990b).

To test the hypothesis that abnormal heart rate is associated with chromosomal abnormalities, we measured embryonic or fetal heart rate in pregnant women who were referred for prenatal counselling.

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## Subjects and methods

We measured fetal heart rate in 424 women, who we saw for prenatal counselling, using an abdominal ultrasound scan (Acuson™ sectorscanner) and pulsed Doppler. In our centre, prenatal counselling precedes prenatal diagnosis by 1–5 weeks. Most of the women (95%) were 36 years or older. In each, blood flow velocity waveforms were obtained from the fetal heart and printed on-line using a strip chart recorder. Ten consecutive signals of good quality were selected and the time between the first and the 10th peak was measured. We expressed fetal heart rate as beats/min. Data were restricted to ten cycles since longer recordings are technically difficult at very early gestation. Moreover, before 16 weeks fetal heart rate accelerations or decelerations are not likely to occur (Wladimiroff 1972). The crown-rump length (CRL) or the biparietal diameter (BPD) was measured during the same session. Ultrasound age was calculated from the reference curves of Robinson (CRL) and of Campbell (BPD). The women selected for this study all had a reliable menstrual history, with a menstrual cycle length between 25 and 35 days. Gestational age was calculated in days from the time since the first day of the last menstrual period (LMP). We performed chorionic villus sampling at 9–10 weeks or amniocentesis at 15–16 weeks gestation.

We compared the heart rates of chromosomally abnormal fetuses with those with normal karyotypes. We made reference ranges for fetal heart rate according to gestational age by the LMP and by ultrasound measurements. This was done as fetuses with chromosomal abnormalities might be small because of slow growth (Fitzsimmons *et al.* 1990).

## Results

Prenatal diagnosis showed a normal karyotype in 414 fetuses. Figures 1 and 2 show heart rate of these fetuses, according to LMP and ultrasound. From these data medians and 10th, 25th, 75th and 90th centiles were calculated (Table 1 and Figs 3 and 4). Median fetal heart rate increased from 138 beats/min at 6 weeks to a peak value of 177 beats/min at 9 weeks. At 16 weeks fetal heart rate had fallen to approximately 150 beats/min.

Fetal karyotyping detected eight autosomal trisomies: five with trisomy 21 and three with trisomy 18 (Table 2). The heart rate of these 8 fetuses was distributed around the median, with no difference between data analysed according to LMP or ultrasound. The fetal heart rate of all Down's syndrome fetuses fell within the normal range (Figs 3 and 4). Two of the three fetuses with trisomy 18 had a fetal heart rate outside the normal range, in one this exceeded the 90th centile (177 beats/min at week 12) and the other was below the 10th centile (142 beats/min at week 7) (Figs 3 and 4).

In two pregnancies mosaic patterns in the chorionic villi were found. In both, a subsequent amniocentesis revealed a normal fetal karyotype (Table 2). The heart rate of both fetuses was, surprisingly, outside the normal range (158 beats/min at week 9 and 185 beats/min at week 10. (Figs. 3 and 4)).

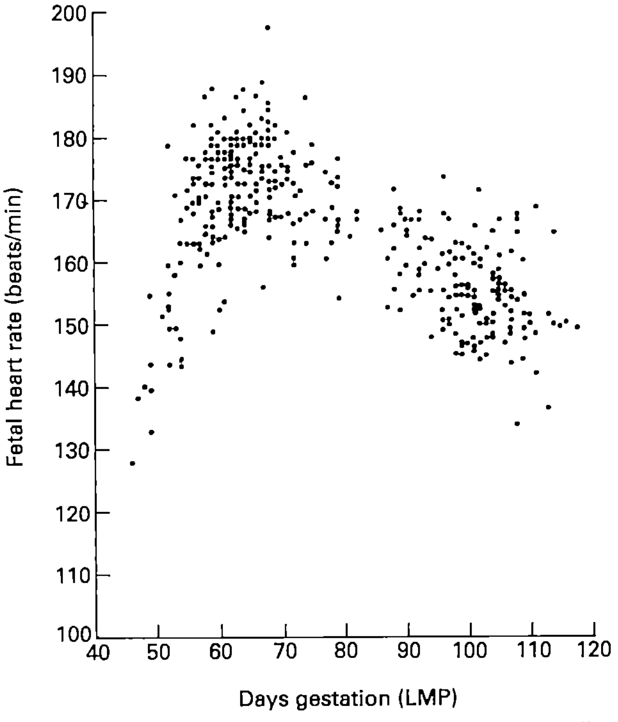

**Fig. 1.** Heart rate of 414 fetuses with a normal karyotype according to gestational age based on last menstrual period (LMP).

## Discussion

With vaginal ultrasound, fetal activity can be detected at about 40 days after the LMP (Timor-Tritsch *et al.* 1988). The time of the first appearance of cardiac activity varies considerably (4 to 5 days) in pregnancies in which the ovulation is exactly known (Cadkin & McAlpin 1984; Schats *et al.* 1990a; Cacciatore *et al.* 1990). A delayed appearance of cardiac activity and an early fetal bradycardia are related to early miscarriage (Laboda *et al.* 1989; Schats *et al.* 1990a). This suggests that an abnormality might result in a delay in early functional development as well as in morphological development.

In fetuses with chromosomal abnormalities there are often signs of early developmental disorders. This is reflected by the high rate of miscarriage, by the delay in morphological growth (weight, femur length) and also by fetal and placental biochemical factors in maternal serum (e.g., alpha-fetoprotein, human chorionic gonadotropin, unconjugated oestriol) (Fitzsimmons *et al.* 1990; Benacerraf *et al.* 1987; Merkatz *et al.* 1984; Bogart *et al* 1987; Canick *et al.* 1988). These findings have led to the hypothesis of a delayed developmental pattern, either morphological, functional or both in chromosomally abnormal fetuses (Cuckle *et al.* 1986; Seller 1990; Kronquist *et al.* 1990). However, abnormal biochemical factors may also be an expression of abnormal placental rather than abnormal fetal development (Van Lith *et al.* 1991).

Disturbed development of the conceptus may be expressed by a delayed onset of fetal cardiac activity. Data on the emergence of cardiac activity in chromosomally abnormal fetuses are restricted to one case report (Schats *et al.* 1990b). In this case heart activity could first be detected at 28 days after follicle aspiration. This is slightly later than observed in normal pregnancy after follicle aspiration (26 to 27 days), but still within the normal range.

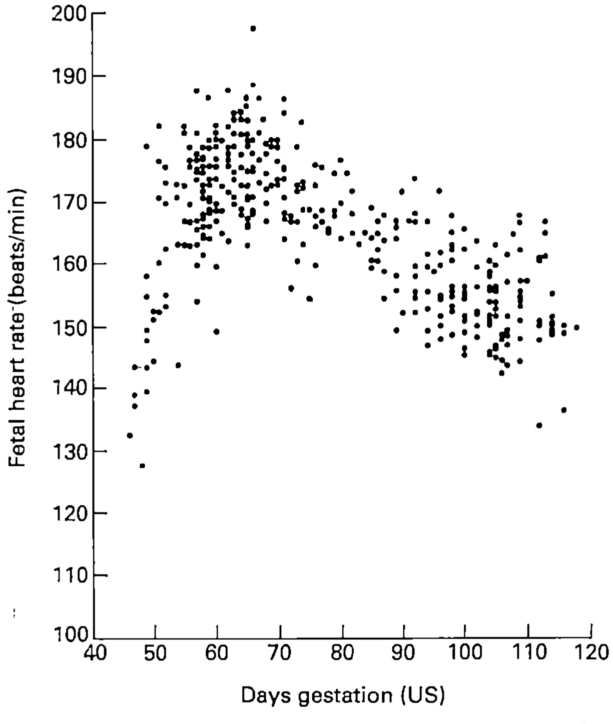

**Fig. 2.** Heart rate of 414 fetuses with a normal karyotype according to gestational age based on ultrasound measurement (US).

**Table 1.** Heart rate in 414 chromosomally normal fetuses expressed as 25th median and 75th centile according to gestational age in completed weeks based on both last menstrual period (LMP) and ultrasound age.

| | Fetal heart rate (beats/min) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | According to LMP | | | | According to ultrasound | | | |
| Gestational age (weeks) | *n* | 25th | Median | 75th | *n* | 25th | Median | 75th |
| 6 | 5 | 129·5 | 139·5 | 145·6 | 6 | 127·7 | 138·9 | 143·5 |
| 7 | 27 | 148·2 | 158·7 | 167·0 | 33 | 152·3 | 163·0 | 172·4 |
| 8 | 85 | 167·2 | 173·1 | 177·0 | 94 | 167·7 | 173·4 | 177·5 |
| 9 | 87 | 170·5 | 177·9 | 179·6 | 61 | 170·5 | 175·4 | 180·5 |
| 10 | 34 | 166·7 | 172·4 | 176·5 | 39 | 166·7 | 172·2 | 175·4 |
| 11 | 18 | 163·9 | 166·7 | 172·4 | 18 | 164·8 | 167·6 | 174·4 |
| 12 | 18 | 157·9 | 163·9 | 167·6 | 23 | 155·6 | 162·9 | 166·7 |
| 13 | 33 | 152·3 | 158·7 | 163·6 | 31 | 152·7 | 157·9 | 161·5 |
| 14 | 63 | 148·5 | 152·9 | 157·9 | 52 | 150·8 | 154·6 | 158·7 |
| 15 | 37 | 149·3 | 154·6 | 158·7 | 38 | 147·8 | 152·2 | 157.1 |
| 16 | 7 | 149·3 | 150·2 | 158·2 | 19 | 148·9 | 150·0 | 160·4 |

Another reflection of abnormal development might be an unusual heart rate in early pregnancy. This hypothesis was tested in this study. The reference ranges for fetal heart rate in early pregnancy that we obtained were similar to those that have been described (Robinson & Shaw-Dunn 1973; Hertzberg *et al.* 1988; Schats *et al.* 1990a).

In our study the heart rate in the eight fetuses with chromosomal disorders did not differ from that in normal fetuses. The use of fetal heart rate for screening is, therefore, not valuable and our findings do not support the suggestion that prenatal diagnosis should be offered whenever an abnormal fetal heart rate is detected early in pregnancy. An abnormal fetal heart rate might be more a marker for a forthcoming miscarriage rather than an indicator for a chromosomal abnormality. Invasive diagnostic procedures should be withheld.

The finding of abnormal heart rates in the two fetuses with a mosaic pattern in chorionic villi is remarkable. Chromosomal mosaicism found in chorionic villi is almost always restricted to the extra-embryonic tissues and the fetus usually has a normal karyotype (Breed *et al.* 1990). However, with a mosaic pattern in the chorionic villi miscarriage and intrauterine growth retardation are more frequent (Johnson *et al.* 1990).

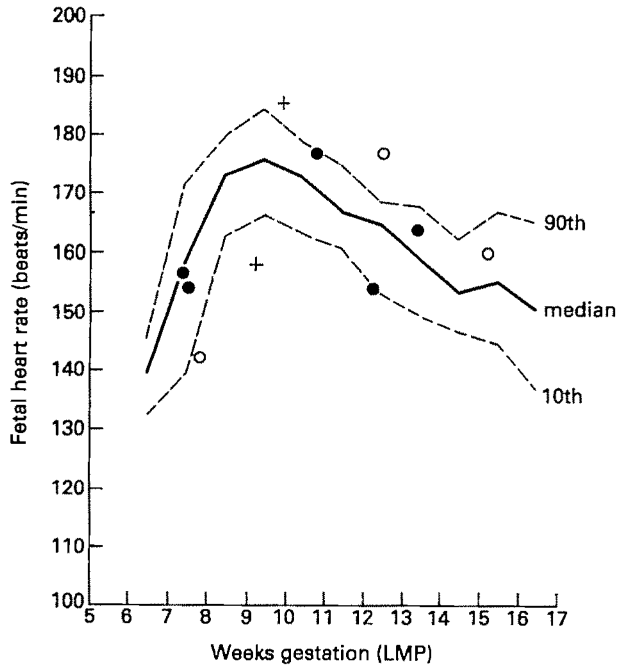

**Fig. 3.** Heart rate of 10 fetuses with abnormal findings after prenatal diagnosis according to gestational age based on last menstrual period (LMP) (trisomy 21 = ●, trisomy 18 = ○, mosaicism in CVS = +). Normal fetal heart rate values are expressed as median and 10th and 90th centile.

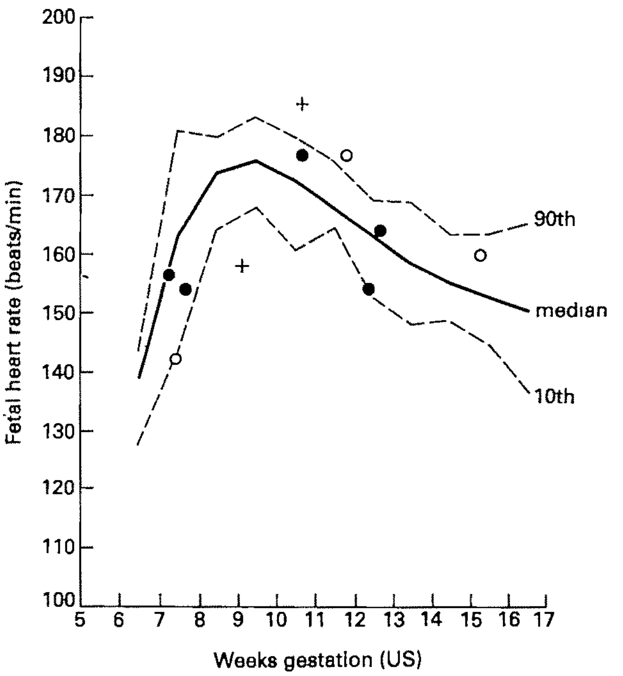

**Fig. 4.** Heart rate of 10 fetuses with abnormal findings after prenatal diagnosis according to gestational age based on ultrasound measurement (US) (trisomy 21 = ●, trisomy 18 = ○, mosaicism in CVS = +). Normal fetal heart rate values are expressed as median and 10th and 90th centile.

**Table 2.** Heart rate of 10 fetuses with abnormal findings after prenatal diagnosis.

| | Gestational age | | |
|---|---|---|---|
| Chromosomal disorder | LMP (days/week) | US (days/week) | Fetal heart rate (beats/min) |
| 47,XY,+21 | 52/ 7 | 51/ 7 | 156·3 |
| 47,XX,+21 | 53/ 7 | 54/ 7 | 153·8 |
| 47,XY,+21 | 79/11 | 75/10 | 176·3 |
| 47,XY,+21 | 86/12 | 87/12 | 153·9 |
| 47,XX,+21 | 94/13 | 89/12 | 163·6 |
| 47,XY,+18 | 55/ 7 | 52/ 7 | 142·1 |
| 47,XX,+18 | 88/12 | 83/11 | 176·5 |
| 47,XX,+18 | 108/15 | 107/15 | 159·6 |
| 46,XX/47,XX,+11 | 65/ 9 | 64/ 9 | 157·9 |
| 46,XY/47,XY,+18 | 70/10 | 75/10 | 185·2 |

LMP = last menstrual period; US = ultrasound measurement.

The abnormal fetal heart rate observed in the two pregnancies with chromosomal mosaicism in chorionic villi supports the concept of disturbed development, though the aetiology of the abnormal heart rate is obscure.

In conclusion, although the number of abnormal chromosomes is small, the heart rates of chromosomally abnormal fetuses in early pregnancy do not appear to be consistently different from those of normal fetuses. A single measurement of fetal heart rate cannot be used as a screening method for identifying fetuses at risk for chromosomal abnormalities. Chromosomal mosaicism in chorionic villi may be associated with abnormal fetal heart rate.

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GYNAECOLOGY

# The prognosis of adenosquamous carcinomas of the uterine cervix

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**ABSTRACT**

**Objectives** Firstly, to identify a cohort of women with invasive adenosquamous carcinomas of the uterine cervix, including mucin-producing squamous cell carcinomas. Secondly, to compare the biological characteristics and behaviour of a cohort of adenosquamous carcinomas with a cohort of non-mucin-producing squamous cell carcinomas.

**Design** Histological review, retrospective survival analysis.

**Setting** Regional multidisciplinary gynaecological oncology service.

**Subjects** 161 cases of stage 1B and above invasive cervical carcinoma presenting between 1 January 1980 and 31 July 1987. Thirty nine women with adenosquamous carcinomas were compared with 103 women with non-mucin-producing squamous cell tumours.

**Results** Inclusion of routine stains for mucin in the assessment of histological material resulted in the reclassification of 38 (24%) of the cases, including the identification of 31 mucin-producing squamous cell carcinomas. The survival with adenosquamous tumours was significantly worse than with squamous cell cancers ($P = 0{\cdot}006$), 5-year survival rates being 52% and 75% respectively. Multivariate analysis showed that this effect was explained by differences in clinical stage, pelvic lymph node metastasis and vascular invasion by tumour.

**Conclusions** The application of routine mucin stains to cervical tumours identifies a group of previously unrecognized adenosquamous cancers. Tumours so identified are likely to pursue a more aggressive clinical course associated with a poorer survial when compared to non-mucin-producing squamous carcinomas.

Traditionally 90–95% of primary tumours of the uterine cervix are classified as squamous cell carcinomas. Tumours with mixed squamous and glandular differentiation have been considered uncommon, comprising less than 5% of cases (Abell 1973). However, recent work has demonstrated the presence of stainable mucin in a significant proportion of cervical squamous carcinomas lacking architectural evidence of glandular differentiation (Shorrock *et al.* 1990; Buckley *et al.* 1988; Ireland *et al* 1987; Benda *et al.* 1985; Yajima *et al.* 1984). Although initially separated as 'mucin-producing squamous carcinomas', these tumours appear to share characteristics with conventional mixed tumours and so warrant inclusion as adenosquamous carcinomas (Buckley & Fox 1989; Hale *et al.* 1991).

The prognosis of patients with adenocarcinoma of the cervix is worse than for patients with squamous cell carcinoma (Kleine *et al.* 1989; Burke *et al.* 1987; Moberg *et al.* 1986; Kjorstad 1977). However, the prognostic significance of adenosquamous tumours, including covert mucin-producing tumours, is not established. The current study reports on the biological behaviour of a cohort of invasive carcinomas of the cervix uterine which included a significant group of adenosquamous tumours.

## Subjects and methods

This study is based on all patients with invasive carcinoma of the cervix, excluding microinvasive tumours, presenting in a health region during the period 1 January 1980 to 31 July 1987. Over this period a regionally based mutidisciplinary approach to the diagnosis and treatment of cervical malignancy was employed (Lamb *et al.* 1990) and a comprehensive registry was maintained by the regional oncology service which served as the sampling frame for this study.

Overall, 186 patients with invasive cervical cancer stage IB and above were identified; 25 were excluded because archival pathology material was either not available (12 patients) or was insufficient for further histological assessment (13 patients). The remaining 161 (87%) were available for study.

All archival material from each case was retrieved; this ranged from small biopsy fragments to comprehensively sampled resection specimens. Representative paraffin blocks were selected from each case, and further sections were cut from these blocks and stained with periodic acid-Schiff(PAS),

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**Table 1.** Original histopathological diagnosis of 161 invasive cervical carcinomas and subsequent classification after routine mucin stains.

| Histological subtype | Number of women (%) | |
|---|---|---|
| | Original | Revised |
| Squamous cell carcinoma | 138 (85·7) | 103 (64·0) |
| Adenocarcinoma | 12 ( 7·5) | 11 ( 6·9) |
| Adenosquamous carcinoma | 5 ( 3·1) | 39 (24·2) |
| Miscellaneous | 6 ( 3·7)* | 8 ( 4·9)** |

*Includes mesonephroid (2), mixed müllerian (2), neuroendocrine (2).
**Includes original cases and 2 undifferentiated tumours.

with diastase pretreatment (to identify neutral mucopolysaccharides) and with alcian blue at pH 2·6 (to identify acidic sulphated mucopolysaccharides).

The mucin-stained sections were examined by two pathologists who had no other information about the case. The amount and distribution of cytoplasmic mucin was recorded. Care was taken to exclude false mucin-positives associated with areas of tumour degeneration or from entrapped benign glandular elements. The haematoxylin & eosin (H & E) stained material was then examined and assessed for squamous and glandular differentiation. A final tumour classification was undertaken using the criteria as set out by Buckley & Fox (1989).

Subsequently, all histological material was examined again to assess other known prognostic factors. Where possible, the maximum depth of tumour spread was measured using a micrometer mounted on a microscope eyepiece objective; an assessment was made of the presence of lymphatic or capillary space involvement and all lymph nodes sampled were re-examined for tumour involvement. In addition, information was abstracted from the registry data base on FIGO clinical stage, tumour bulk as determined by examination under anaesthesia, age at diagnosis, and the nature of surgery, and/or external or intracavity radiotherapy undertaken.

Detailed survival information was available from the registry; survival was calculated from the date of diagnosis to the date of last follow-up, intercurrent death or cervical cancer-related death. In addition, data on local tumour recurrence were abstracted. Survival was analysed in an acturial manner using the product-limit method of Kaplan and Meier (1958). Univariate survival analysis was assessed using the log-rank test and multivariate analysis was undertaken using the proportional hazard modelling described by Cox (1972).

## Results

As a result of mucin staining, we revised the original classification in 38 of the 161 cases (24%) (Table 1). All of the original 12 cases classified as adenocarcinomas demonstrated glandular features associated with prominent globular cytoplasmic and/or luminal acidic and neutral mucins. On review three of the cases had, in addition, distinct areas of squamous differentiation and so were reclassified as well-differentiated mixed tumours. The original five mixed carcinomas were well differentiated adenosquamous tumours showing clear evidence of mixed glandular and squamous components on H & E and mucin staining.

Two cases initially labelled as poorly differentiated squamous cell carcinomas lacked evidence of squamous differentiation on review and demonstrated cytoplasmic staining for both neutral and acid mucopolysaccharides in at least 75% of the tumour cells and were therefore poorly differentiated adenocarcinomas (Fig. 1). Two poorly differentiated squamous tumours were reclassified as undifferentiated, as these lacked any evidence of squamous or glandular differentiation.

On H & E, morphology 134 cases showed squamous differentiation without obvious glandular features. However, routine mucin staining revealed focal mucin-positives in 31 of them. In all these tumours, the mucin-positive cells comprised less than 25%, and in most of them less than 10%, of the tumour cell population. In 10 specimens there were distinct cytoplasmic globules which stained for both acidic and neutral mucins and these were classified as strongly positive (Fig. 2). There were 24 cases showing weakly positive, less intense and more dif-

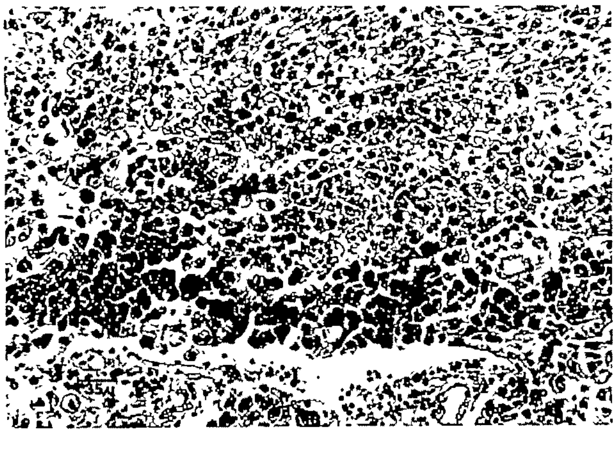

**Fig. 1.** This invasive tumour was previously classified on H & E stained material as a poorly differentiated squamous cell carcinoma. On staining for mucin, the majority of the tumour cells contain cytoplasmic mucin. (PAS–diastase).

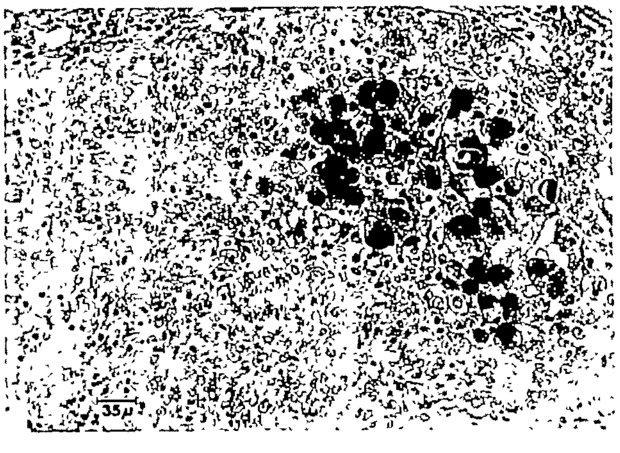

**Fig. 2.** This invasive tumour was previously classified on H & E stained material as a moderately differentiated squamous cell carcinoma. Mucin staining identifies a distinct sub-population of tumour cells containing cytoplasmic mucin. (PAS-diastase).

**Table 2.** Characteristics of the subgroups of adenosquamous (*n*=39) and non-mucin-producing squamous cell carcinomas (*n*=103).

| | Adenosquamous carinomas *n* (%) | Squamous cell carcinomas *n* (%) | Test statistic | | |
|---|---|---|---|---|---|
| | | | $\chi^2$ | *t* | *P* |
| FIGO stage | | | | | |
| IB | 19 (49) | 62 (60) | 13·6 | *n* | 0·004 |
| IIA | 9 (23) | 11 (11) | | | |
| IIB | 8 (2) | 6 (6) | | | |
| III,IV | 3 (7) | 24 (23) | | | |
| Pelvic lymph node involvement | | | | | |
| Present | 9 (31) | 14 (22) | 0·8 | *n* | 0·35 |
| Absent | 20 (69) | 49 (78) | | | |
| Lymphatic capillary space involvement in primary tumour | | | | | |
| Present | 13 (39) | 27 (28) | 1·6 | — | 0·20 |
| Absent | 20 (61) | 71 (72) | | | |
| Tumour size (mm) | | | | | |
| Mean (SD) | 37·2 (16·7)<br>(*n*=31) | 35·0 (15·4)<br>(*n*=91) | — | 0·66 | 0·50 |
| Maximum depth of invasion (mm) | | | | | |
| Mean (SD) | 8·7 (3·8)<br>(*n*=21) | 8·7 (3·9)<br>(*n*=82) | — | 0·03 | 0·97 |
| Age (years) | | | | | |
| Mean (SD) | 46·4 (13·4) | 50·1 (14·9) | — | 1·66 | 0·08 |

Results are number (%) of women or mean (SD) values as appropriate.

fuse cytoplasmic staining, identified by both PAS-diastase and alcian blue stains; an additional 10 demonstrated scattered fine granular cytoplasmic positiveness on PAS-diastase staining but lacked staining for acid mucins; these 34 cases were thought to have non-specific staining of lysosomal bodies in degenerate cells and were considered to be mucin-negative.

Therefore, 39 cases of adenosquamous carcinoma (8 well- and 31 poorly-differentiated) were available for comparison with 103 cases of non-mucin-producing squamous cell carcinomas. The numbers in the other histological subtypes were too small for meaningful analysis.

The descriptive characteristics and biological behaviour of the two groups are summarized in Table 2. Sufficient material to assess the presence of lymphatic or capillary space invasion by tumour was available for 92%; nodal status was available in 92 cases where lymph nodes were sampled at operation. An average of 17 nodes were sampled, and involved nodes were detected in 23 cases. The nodal pattern was different in these two groups: among the squamous cell tumours, all were confined to 'first station' nodes (paracervical, obturator and external iliac), whereas five of nine in the adenosquamous group had spread to additionally involved second station nodes (sacral common iliac, inguinal).

### *Survival analysis*

Nine of the women died of causes other than cervical cancer. These included five with other malignancies (breast in one, colorectal in two, lung in one and chronic granulocytic leukaemia in one). Of the other four women, two died in motor vehicle accidents, one of alcoholic liver disease and one of diabetic nephropathy. These intercurrent deaths were censored in the survival analysis. Table 3 summarizes the univariate effects of measured variables on survival. The survival experience was significantly different for women with the two histological tumour subtypes (log rank, *P*=0·006) (Fig. 3). The crude 5-year survival rate for non-mucin-producing squamous carcinomas was 75% compared with 52% for adenosquamous tumours.

A significant difference in time to local recurrence was also demonstrated between adenosquamous and non-mucin-producing squamous tumours (log rank, $\chi^2$ = 6·4, *P*=0·01). The recurrence rate at 12, 24 and 36 months for non-mucin-producing squamous tumours was 6%, 9% & 11% (women at risk 85, 74, 65 respectively) and for the adenosquamous tumours 14%, 24% & 29% (women at risk 27, 19, 13 respectively).

The multivariate analysis of potential prognostic factors using stepwise Cox proportional hazard modelling is described in Table 4. Two models are presented: firstly, an overall model of potential prognostic factors, and secondly, a model based on the subset of women where pelvic lymph node status, which was assessed as a result of surgical treatment (92 cases). These models show that after mutivariate adjustment, the significant difference in survival between the histological subtypes is lost. Clinical stage, vascular invasion and pelvic lymph node metastasis remain as independent predictors of survival.

## Discussion

Histogenically, the majority of cervical malignancies are believed to arise from the reserve stem cell of the transition zone epithelium (Teshima *et al.* 1985). Therefore, differentiation towards squamous, glandular or a mixed pattern is not surprising. Similar patterns of divergent differentiation can be seen in other tumours of mullerian and non-mullerian epithelium such as endometrial, transitional and bronchogenic carcinomas. Traditionally, mixed cervical carcinomas were relatively uncommon; however, as confirmed by the current study, a significant number of invasive cervical tumours with-

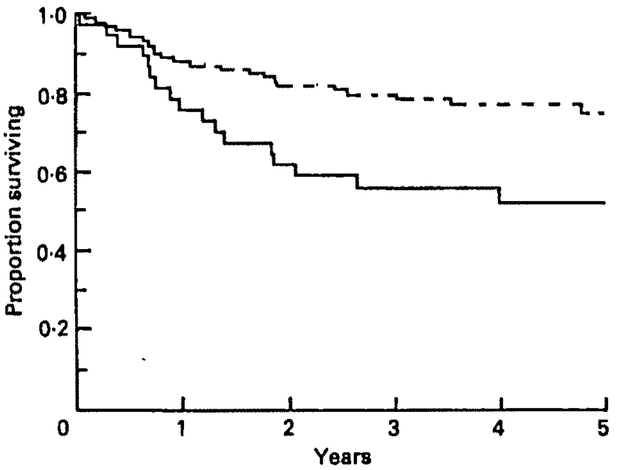

**Fig. 3.** Five-year actuarial survival curve by tumour subtype. The number of patients at risk at entry and at 1 through 5 years are 103, 86, 78, 70, 56 & 28 for the squamous cancers and 39, 28, 22, 18, 14 & 9 for the adenosquamous group. - - - non-mucin-producing squamous carcinomas (*n*=103); —— adenosquamous carcinomas (*n*=39).

**Table 3.** Five-year survival proportions in 142 women with invasive cervical carcinoma — Prognostic factors, univariate analysis.

| Factor | Grouping | Total numbers | 5-year survival proportion | Statistics<br>Log-rank $\chi^2$ | Statistics<br>$P$ |
|---|---|---|---|---|---|
| Histology | Squamous | 103 | 0·75 | 7·2 | 0·006 |
| | Adenosquamous | 39 | 0·52 | | |
| Squamous grade | Well | 13 | 0·85 | 1·4 | 0·40 |
| | Moderate | 57 | 0·69 | | |
| | Poor | 33 | 0·79 | | |
| Adenosquamous grade | Well | 8 | 0·68 | 0·9 | 0·46 |
| | Poor | 31 | 0·49 | | |
| Mucin production | Weak (+) | 24 | 0·46 | 1·6 | 0·20 |
| | Strong (+ +) | 15 | 0·61 | | |
| Stage | I | 81 | 0·78 | 12·9 | 0·002 |
| | II | 34 | 0·65 | | |
| | III,IV | 27 | 0·46 | | |
| Age (years) | <40 | 48 | 0·79 | 2·9 | 0·09 |
| | ≥40 | 94 | 0·64 | | |
| Tumour size (mm) | <30 | 70 | 0·67 | 0·005 | 0·88 |
| | ≥30 | 52 | 0·69 | | |
| Depth of invasion (mm) | <10 | 71 | 0·76 | 4·8 | 0·02 |
| | ≥10 | 32 | 0·51 | | |
| Lymphatic/capillary space involvement | Present | 40 | 0·50 | 8·2 | 0·004 |
| | Absent | 91 | 0·81 | | |
| Pelvic lymph node status | Involved | 23 | 0·56 | 10·9 | 0·001 |
| | Not involved | 69 | 0·88 | | |
| Treatment | Surgery | 16 | 0·92 | 12·7 | 0·01 |
| | Radiotherapy | 37 | 0·60 | | |
| | Combined | 81 | 0·75 | | |
| | Palliative | 8 | 0·00 | | |

out architectural evidence of glandular differentiation show mucin production (Shorrock *et al.* 1990; Buckley & Fox 1988; Ireland *et al.* 1987; Benda *et al.* 1985; Yajima *et al* 1984). The majority of these tumours share features of squamous differentiation and therefore warrant the designation of mixed or adenosquamous carcinomas. Previously, workers have made a distinction between well differentiated mixed tumours (mucoepidermoid type) and poorly differentiated types (mucin secreting squamous carcinomas, glassy cell tumours and the like) (Buckley *et al.* 1988). In the current study mixed tumours demonstrating either strong or weak mucin expression behaved similarly, supporting a unified concept for mixed tumours (Buckley & Fox 1989; Hale *et al.* 1991).

Previous studies have differed in the criteria applied to identify significant mucin production. Some have accepted any slight evidence of mucin secretion as positive (Shorrock *et al.*

**Table 4.** Relative risk for deaths of invasive carcinoma (Cox proportional hazard regression). Model I is an overall model of potential prognostic factors, model II is on the subset of 73 women in whom pelvic lymph node status was assessed.

| Variable | Model I ($n$=107)*<br>Relative risk | Model I ($n$=107)*<br>95% CI | Model I ($n$=107)*<br>$t$ | Model II ($n$=73)*<br>Relative risk | Model II ($n$=73)*<br>95% CI | Model II ($n$=73)*<br>$t$ |
|---|---|---|---|---|---|---|
| Histological type | | | | | | |
| Adenosquamous | 2·17 | 0·89–5·27 | 1·83 | 2·66 | 0·84–8·38 | 1·67 |
| Squamous | 1·00 | | | 1·00 | | |
| Stage | | | | | | |
| I | 1·00 | | | 1·00 | | |
| II | 1·19 | 0·47–3·06 | 0·38 | 1·21 | 0·33–4·34 | 0·29 |
| III, IV | 4·00 | 1·58–10·13 | 2·93 | 17·58 | 1·65–188·1 | 2·37 |
| Lymphatic/capillary invasion | | | | | | |
| Present | 2·55 | 1·24–5·28 | 2·55 | 3·91 | 1·17–15·15 | 1·97 |
| Absent | 1·00 | | | 1·00 | | |
| Pelvic nodal involvement | | | | | | |
| Present | — | — | — | 5·39 | 1·4–20·61 | 2·55 |
| Absent | — | — | — | 1·00 | | |

*non-significant: grade, age, tumour size, depth of invasion, treatment type.

1990), while others have laid down more strict criteria for acceptable cytoplasmic mucin (Buckley *et al.* 1988). We have taken a conservative approach, believing that many of the tumour cells which are fine-granular, PAS-diastase positive represent degenerate cells. In these cases there were no positives for acidic mucins on alcian blue staining, thus supporting this contention. The most common staining pattern was of a weak co-expression of acid and neutral mucins which is different in character from that seen in classical adenocarcinomas. However, there was no difference in survival profile between the weakly and strongly positive cases (see Table 3), lending weight to the argument that both represent real mucin production.

The majority of studies, including several large series, demonstrate that cervical adenocarcinomas have a less favourable outlook than squamous carcinomas (Kleine *et al.* 1989; Burke *et al.* 1987; Moberg *et al.* 1986; Kjorstad 1977). Some authors have analysed separately the behaviour of adenosquamous tumours and the results are conflicting with investigators either reporting no differences in prognosis when compared with pure squamous or adenocarcinomas (Yazigi *et al* 1990; Kilgore *et al.* 1988; Hopkins *et al.* 1988) or finding a worse outlook (Saigo *et al.* 1986; Gallup *et al.* 1985; Fu *et al.* 1982). Comparability across studies is limited by the different criteria used to define adenosquamous tumours. However, using the broad definition of adenosquamous tumours to include both well and poorly differentiated types, other workers have shown that these tumours display more aggressive characteristics, including a high prevalence of lymph node metastasis (Buckley *et al.* 1988; Ireland *et al.* 1987). The current study extends these findings to show a distinctly poorer survival among women with an invasive mixed tumour compared with those who have an invasive squamous carcinoma. Multivariate analysis shows that histological subtype is not an independent predictor of survival and that the survival difference between mucin and non-mucin-producing tumours is explained by differences in clinical stage, nodal status and vascular invasion.

The presence of vascular space permeation by cervical tumours is associated with nodal metastases and a poor outlook (Buckley *et al.* 1988; Hopkins *et al.* 1988; Friedell *et al.* 1967). In the current series, among those women where lymph nodes were sampled, vascular invasion predicted poorer survival independent of lymph node status. Lymphatic/capillary space involvement is likely to be underestimated significantly in many cases as the invasion front is often not well sampled in biopsy material. Because of the importance of this variable as a predictor of ultimate outlook, a more formal identification of vascular spaces using immunohistochemical techniques may be warranted.

Less is known of the risk factors for adenocarcinoma and adenosquamous tumours than their squamous counterparts. The relative frequency of well and moderately-well differentiated adenocarcinomas compared to squamous cell carcinomas is increasing, especially in younger patients (Webb & Sheehan 1989) and a relation with hormonal contraception (Chilvers *et al.* 1987) and pregnancy (Glucksmann 1957) has been proposed. Using a range of techniques, workers have shown differences in subtypes of human papillomavirus (HPV) DNA present in cervical adenocarcinomas and squamous carcinomas, with well differentiated adenosquamous tumours having an intermediate distribution of HPV subtypes (King *et al.* 1989; Tase *et al.* 1988; Smotkin *et al.* 1986). More work is needed to define the risk factors associated with differentiation towards mucin production with its attendant affect on tumour behaviour.

In conclusion we have shown that in a series of invasive cervical carcinomas, use of mucin stains identifies a significant group of adenosquamous tumours, the majority of which are mucin-producing squamous cell carcinomas. When compared with non-mucin-producing squamous tumours, women with adenosquamous cancers have a significantly higher rate of local tumour recurrence and poorer survival. The survival difference between the two groups is explained by effects of clinical stage, nodal spread and vascular space involvement. Routine mucin staining allows the pathologist to easily and cheaply identify a group of aggressive cervical tumours and further work should now follow on the biology, epidemiology and appropriate treatment of these mixed tumours.

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GYNAECOLOGY

# Endometrial responses in artificial cycles: A prospective study comparing four different oestrogen dosages

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**ABSTRACT**

**Objective** To examine the endometrial response to four different regimens of oestrogen.

**Design** A prospective, randomized cross-over study.

**Setting** Jessop Hospital for Women, Sheffield.

**Subjects** Twenty one women with premature ovarian failure divided into three equal groups.

**Interventions** Four different regimens of hormone replacement therapy: variable, fixed 1 mg, fixed 2 mg and fixed 4 mg oestrogen dosages. Each woman received the variable dosage regimen in one cycle and crossed over to receive one of the three fixed dose regimens (1 mg, Group 1; 2 mg, Group 2; 4 mg Group 3) in another cycle.

**Main outcome measure** Ultrasonographic measurement of endometrial thickness and outpatient endometrial biopsy on day 19 of the artificial cycle; analysis of endometrial specimens by three separate methods: traditional histological criteria, morphometry and immunohistochemistry.

**Results** The endometrial response was similar in those treated with the variable and the fixed 2 mg or 4 mg dosage regimens. The response was suboptimal in those treated with the fixed 1 mg dosage regimen.

**Conclusions** Normal endometrial development requires adequate priming of the endometrium by oestrogen, which may be administered in a sequential, variable dosage fashion, or simply by a fixed daily dosage regimen. However, the minimum daily dose required is likely to be 2 mg of oestradiol valerate. No adverse effect on the endometrium was observed at a daily dose of 4 mg oestradiol valerate, which produced plasma levels of oestradiol above the reference ranges of the natural cycle.

There is little doubt that normal endometrial development in the luteal phase is of crucial importance to successful implantation, and this is, in turn, dependent on adequate amounts of steroid hormones. Whereas it is generally accepted that subnormal amounts of progesterone result in abnormal endometrial development, supraphysiological doses of progesterone do not appear to advance normally developing endometrium (Li *et al.* 1992a).

However, the effect of various levels of oestrogen in the follicular phase (oestrogen priming) on subsequent development of the endometrium in the luteal phase is less clear, partly because the administration of oestrogen in the follicular phase may have a number of different effects at various levels of the hypothalamic-pituitary-ovarian-endometrial axis. To examine the direct effect of various doses of oestrogen on endometrial development, we conducted a prospective study to examine the endometrial response to various predefined doses of oestrogen in a group of women with premature ovarian failure (POF). In this way, any indirect effect of oestrogen via the hypothalamus-pituitary-ovarian axis on the endometrium could be eliminated. In particular, we wished to compare the hormone replacement therapy regimen proposed by Navot *et al.* (1986) (which is known to be capable of producing normal endometrial development and supporting implantation) in which the oestrogen was administered in a sequential, variable dose fashion to mimic the changes in the natural cycle, to regimens in which the daily dose of oestrogen was fixed. The endometrial response was assessed by transabdominal ultrasonographic measurement of its thickness, the traditional histological dating criteria (Noyes *et al.* 1950), established morphometric techniques (Li *et al.* 1988) and an immunohistochemical technique using an antibody raised against an endometrial mucin (Smith *et al.* 1989).

## Subjects and methods

The study involved 21 women attending the premature ovarian failure clinic at the Jessop Hospital for women for hormone replacement therapy and donor oocyte treatment. Premature ovarian failure was defined as amenorrhoea for ≥6 months, associated with persistently low plasma oestradiol (<100 pmol/l) and elevated plasma follicle stimulating hor-

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mone (FSH) (>20 iu/l), in a woman under 40 years of age (Mattison *et al.* 1984). All of the women had chromosomal analysis and estimations of plasma antiovarian antibody. Previous hormone replacement therapy was not an inclusion criterion. The 21 women were randomly divided by lottery into three equal groups. Each woman was treated with Cyclo-Progynova (oestradiol valerate 2 mg/day, on days 1–21; norgestrel 500 mg/day, on days 12–21) (Schering, Sussex, UK) in a pre-study cycle followed by two study cycles: one with a standard hormone replacement therapy regimen (variable oestrogen doses) (Navot *et al.* 1986) and the other with one of the three alternative regimens with fixed daily doses of oestradiol valerate (1 mg, 2 mg or 4 mg) (Table 1). The standard and alternative regimens differ only in the oestrogen doses, while the progesterone doses were the same in all these regimens.

The seven women in the first group received the standard HRT regimen in one cycle, and the fixed 1 mg oestrogen dose regimen in another cycle; the seven women in the second group received the standard HRT regimen in one cycle and the fixed 2 mg oestrogen dose regimen in another cycle and the seven women in the third group received the standard HRT regimen in one cycle and the fixed 4 mg oestrogen dose regimen in another cycle. Thirteen women received the standard regimen in the first cycle and the allocated fixed dose regimen in a subsequent cycle; whereas the other eight received one of the fixed dose regimens in the first cycle and crossed-over to the standard dose regimen in a subsequent cycle.

On days 15, 19 and 29 of the study cycles, a 10 ml sample of blood was taken for assay of plasma oestradiol and progesterone. The endometrial thickness was measured by ultrasonography, and an outpatient endometrial biopsy was performed on day 19 of the study cycles.

*Hormone assays*

Progesterone was assayed by non-extraction, solid phase radioimmunoassay (RIA) using $^{125}$I as a marker (Diagnostic Products Limited, Abingdon, Oxon). The sensitivity of the assay was 0·16 nmol/l and the mean intra- and inter-assay coefficients of variation were 7·2% and 7·9%, respectively.

Oestradiol was assayed by non-extraction, solid phase radioimmunoassay (RIA) using $^{125}$I as a marker (Diagnostic Products Limited, Abingdon, Oxon). The sensitivity of the assay was 29 pmol/l and the mean intra- and inter-assay coefficients of variation were 5·4% and 6·4%, respectively.

**Table 1.** Doses of oestradiol valerate and progesterone administered in the standard (variable) and fixed dose hormone replacement regimens.

| | Oral oestradiol valerate (mg) | | | | |
|---|---|---|---|---|---|
| Day of cycle | Standard regimen* | Fixed dose regimens 1 mg | 2 mg | 4 mg | Intramuscular progesterone (mg) |
| 1–5 | 1 | 1 | 2 | 4 | – |
| 6–9 | 2 | 1 | 2 | 4 | – |
| 10–13 | 6 | 1 | 2 | 4 | – |
| 14 | 2 | 1 | 2 | 4 | – |
| 15–16 | 2 | 1 | 2 | 4 | 25 |
| 17 | 2 | 1 | 2 | 4 | 50 |
| 18–26 | 4 | 1 | 2 | 4 | 50 |
| 27–28 | 1 | 1 | 2 | 4 | 25 |
| 29 | – | – | – | – | – |

*The standard HRT regimen was the same as that proposed by Navot *et al.* (1986).

*Ultrasonography*

This was performed by a transabdominal real-time scanner (Combison 320, Kretztechnik, Zipf, Austria). The maximum thickness of the endometrium on longitudinal section was measured three times, and the mean value obtained was used for subsequent calculation. The ultrasonography was performed by two observers, with an inter-observer coefficient of variation of about 8%. The endometrium was measured from the echogenic interface of the junction of the endometrium and myometrium and the measurement represents the two layers of endometrium (Li *et al.* 1992b).

*Endometrial biopsy*

Endometrial biopsies were obtained as an outpatient procedure using a Sharman's curette (Down Surgical Ltd., Sheffield, UK). A single endometrial specimen was obtained from the fundus and upper part of the body of the uterus. Each specimen was fixed immediately in 2% glutaraldehyde in cacodylate buffer (pH 7·4) for 4–6 h. It was then washed in buffer, dehydrated and embedded in JB-4 (Polysciences, Inc., Warrington, Pennsylvania, USA), a plastic polymer. The specimen was sectioned at 2 μm, and the sections were stained with acid fuchsin and Toluidine Blue for examination by light microscopy.

All the endometrial biopsies were examined histologically by three different methods: (a) the traditional dating criteria (Noyes *et al.* 1950); (b) morphometry i.e., quantitative measurements, the details of which have been described previously (Li *et al.* 1988; Dockery *et al.* 1990). The mean stromal cell diameter was measured using a digitizing tablet (Calcomp 'bit pad') linked to a microcomputer and the volume fraction of endometrium occupied by stromal cell nuclei was estimated by point counting (Weibel 1979); and (c) immunohistochemistry using monoclonal antibody D9B1 raised against a secretory mucin produced by endometrial glands (Smith *et al.* 1989).

*Ethical aspects*

Informed consent was obtained from each woman participating in the study. Approval for this study had been obtained from the ethics committee of the former Southern District of the Sheffield Health Authority.

*Statistics*

Comparisons of results within an individual were made using the Wilcoxon matched-pair non-parametric test. This was performed on the Statistical Package for Social Sciences (SPSS-X).

## Results

The characteristics of the women in this study, including the diagnosis and duration of premature ovarian failure, age, weight, height, body mass index (weight/height$^2$), and duration of HRT, are shown in Table 2. Although women in the third group appeared to be the youngest, thinnest with the least body mass index, longest duration of POF and HRT, there were no significant differences in any of these characteristics between the three groups of women.

Plasma oestradiol concentrations on days 15, 19 and 29, and plasma progesterone concentration on day 19, of cycles treated with the various HRT regimens are shown in Fig. 1. As expected, there was no difference in plasma progesterone concentrations between the various treatment cycles, but plasma oestradiol concentrations were highest in cycles treated with the fixed 4 mg oestrogen dose and lowest with the fixed 1 mg oestrogen dose.

The results of ultrasonographic measurement of endometrial thickness, histological dating according to the traditional criteria (Noyes *et al.* 1950), morphometric analysis and immunohistochemical study of the glandular secretory activities of the endometrium are shown in Fig. 2. Significant differences were found between cycles treated with the standard regimen and the fixed 1 mg oestrogen regimen in a number of morphological and immunohistochemical measurements. However, there were no differences between cycles treated with the standard and fixed 2 mg doses, and between the standard and fixed 4 mg doses. Other results of morphometric analysis on mitotic activity and the stromal component of the endometrium are summarized in Table 3.

Typical appearances of the endometrial glands in cycles treated with the variable oestrogen dosage regimen and the fixed 1 mg dosage regimen are shown in Fig. 3 (see p. 755).

## Discussion

In this study, we examined the effect of four different HRT regimens (with various oestrogen doses) on endometrial development on day 19 of the artificial cycle in women with premature ovarian failure. We chose subjects with non-functioning ovaries because they do not produce any significant amount of steroid hormones in their ovaries, and so any observable change in endometrial response is unlikely to be a consequence of changes in endogenous steroid hormone production, but almost certainly a direct consequence of the varying doses of steroid hormones administered.

A special feature of the present study was the cross-over design in which each subject received the standard, variable oestrogen dose regimen in one cycle and one of the fixed oestrogen dose regimens in another cycle; the comparison of these paired-results within each subject reduced any potential error due to bias in selection of subjects or variation in results due to differences in individual responses to steroid hormone. This is particularly relevant as it has been shown that there is a significant inter-subject variation in the endometrial response to a standard HRT in artificial cycles (Fraser *et al.* 1989; Li *et al.* 1991).

Most previous studies on the endometrial response to HRT in artificial cycles were based on histological analysis using the traditional dating criteria; none of them employed quantitative histological techniques. We have examined the morphological responses of both the glandular and stromal components of the

**Table 2.** The characteristics of the three study groups with premature ovarian failure (POF) who were treated with the variable oestrogen hormone replacement therapy (HRT) regimen in one cycle, and crossed-over to receive a fixed oestrogen dose regimen in another cycle (Group 1: 1 mg; Group 2: 2 mg; Group 3: 4 mg).

| Variable | Group 1 (*n* = 7) | Group 2 (*n* = 7) | Group 3 (*n* = 7) |
|---|---|---|---|
| Diagnosis of POF | | | |
| Idiopathic | 5 | 7 | 4 |
| Chemotherapy | 1 | 0 | 1 |
| Turner's syndrome | 1 | 0 | 2† |
| Age (years) | 33 | 33 | 29 |
| | (28–37) | (27–37) | (27–37) |
| Weight (kg) | 58·0 | 68·0 | 54 4 |
| | (47·7–69·0) | (50·9–74·8) | (44·0–68·7) |
| Height (m) | 1·63 | 1·68 | 1·58 |
| | (1·50–1·72) | (1·63–1·72) | (1·50–1·73) |
| Body mass index (kg/m$^2$) | 23·0 | 23·9 | 21·2 |
| | (19·3–24·1) | (18·0–26·3) | (18·0–26·8) |
| Duration of POF* (years) | 2 | 2 | 5 |
| | (1–9) | (1–17) | (1–11) |
| Duration of HRT (months) | 18 | 4 | 24 |
| | (1–96) | (1–24) | (2–120) |

Results are median values with ranges in brackets.
*Excluding those with primary amenorrhoea.
†One had Turner's mosaic xo/xx.

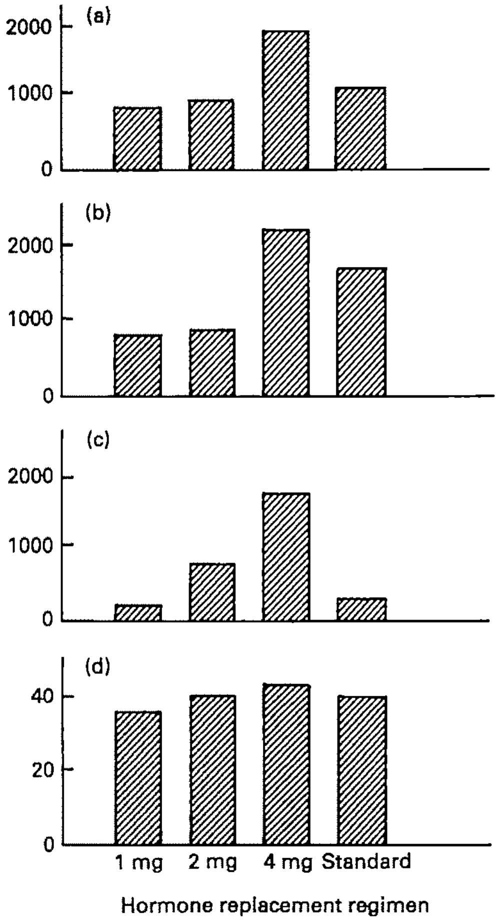

**Fig. 1.** Median plasma oestradiol concentrations (pmol/l) on (a) day 15, (b) day 19 and (c) day 29, and (d) plasma progesterone concentration (nmol/l) on day 19 of artificial cycles in women treated with four different hormone replacement regimens (see text).

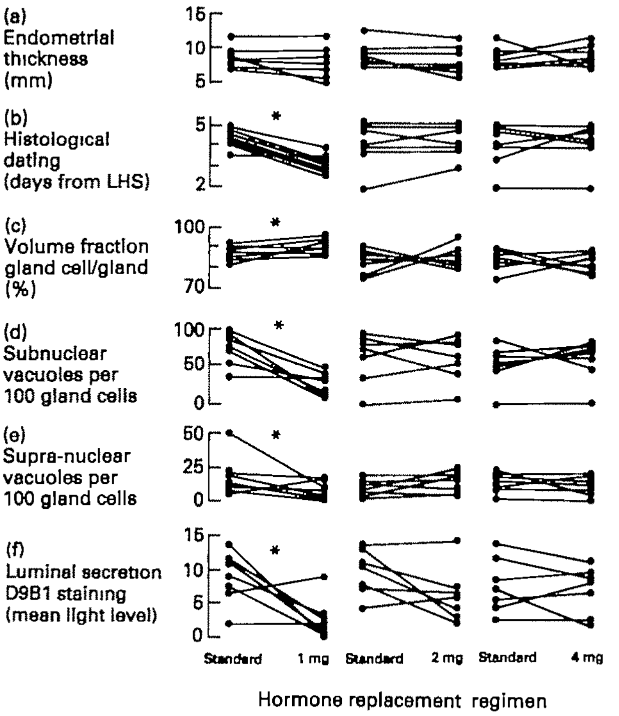

**Fig. 2.** Endometrial response on day 19 of the artificial cycle to one of four different oestrogen dose regimens. Each group received the standard variable oestrogen dose regimen in one cycle and one of three fixed oestrogen dose regimens (1 mg, 2 mg and 4 mg) in another cycle. (a) endometrial thickness as measured by ultrasonography; (b) histological dating based on the traditional criteria; (c) to (e) morphometric analysis of glandular secretory activity; (c) volume fraction of gland occupied by gland cells (%); (d) number of subnuclear secretory vacuoles per 100 gland cells; (e) number of supranuclear vacuoles per 100 gland cells; and (f) immunohistochemical assessment of secretory activity in the gland lumen by reflected light measurement, using an antibody D9B1 raised against an endometrial glycoprotein. *Significant difference between matched pairs ($P<0{\cdot}05$, Wilcoxon matched pair test).

endometrium to various oestrogen doses by established morphometric techniques, in addition to the use of the traditional dating criteria (Noyes *et al.* 1950) as well as established immunohistochemical technique. It is of interest to note that these various methods of analysis produced rather similar results (Fig. 2). The results of ultrasonographic assessment of endometrial thickness did not, however, correlate well with other methods of assessment. This is perhaps not surprising, as it has been shown that ultrasonographic measurement of endometrial thickness does not reflect accurately histological development of the endometrium (Li *et al.* 1992b).

### *Variable compared with fixed oestrogen dosage regimens*

The HRT regimens proposed by Lutjen *et al.* (1984) and Navot *et al.* (1986) were designed to mimic the natural cycle, and so the oestrogen was administered in a variable, incremental manner to reproduce an oestrogen surge in the late follicular phase. However, it is not clear whether such a variable regimen is required for normal endometrial maturation. Our findings showed similar endometrial responses to the variable and fixed 2 mg and 4 mg oestrogen dose regimens and provide evidence to suggest that normal endometrial development is not dependent on incremental changes in oestrogen concentration, such as the oestrogen surge in the late proliferative phase. Serhal & Craft (1989) reported successful pregnancies in a donor oocyte programme in which recipients were treated with a fixed oestrogen dose regimen. Thus, there is now both clinical and scientific data to indicate that the variable, incremental regimen may be simplified to a fixed oestrogen dose regimen. The latter is simple and therefore likely to increase patient compliance.

### *Various oestrogen doses*

Although normal endometrial development could be achieved with the fixed 2 mg or 4 mg oestrogen regimens, we found that endometrial development in cycles treated with the fixed 1 mg oestrogen dose regimen had significantly less advanced overall endometrial maturity (histological dating) than those treated

**Table 3.** Morphometric analysis of mitotic activity and the stromal component of the endometrium in three groups of women treated with four different oestrogen dosage regimens.

| | Hormone replacement regimen | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 (*n* = 7) | | Group 2 (*n* = 7) | | Group 3 (*n* = 7) | |
| Morphometric variables | Standard | Fixed 1 mg | Standard | Fixed 2 mg | Standard | Fixed 4 mg |
| Mitoses per 1000 gland cells | 1<br>(0–1) | 0 | 0<br>(0–1) | 0<br>(0–1) | 0<br>(0–1) | 0<br>(0–1) |
| Mitoses per 1000 stromal cells | 1<br>(0–1) | 0 | 0<br>(0–1) | 1<br>(0–1) | 1<br>(0–1) | 0<br>(0–2) |
| Volume fraction of endometrium occupied by stromal cell nuclei (%) | 0·12<br>(0·07–0·16) | 0·15<br>(0·09–0·16) | 0·12<br>(0·10–0·17) | 0·13<br>(0·10–0·21) | 0·13<br>(0·07–0·14) | 0·14<br>(0·12–0·16) |
| Mean diameter of stromal cells (μm) | 5·05<br>(4·36–5·77) | 5·53<br>(4·49–6·07) | 5·32<br>(4·86–5·77) | 5·68<br>(4·62–6·61) | 5·25<br>(4·86–6·51) | 5·04<br>(4·58–5·39) |
| Ratio of maximum to minimum diameter of stromal cells | 1·73<br>(1·51–2·45) | 1·83<br>(1·63–2·78) | 1·74<br>(1·48–2·45) | 1·76<br>(1·67–2·26) | 1·74<br>(1·61–2·47) | 1·74<br>(1·53–2·05) |

Results shown are medians with ranges in brackets.
Each group of women received the standard (variable oestrogen) regimen in one cycle and one of the three fixed oestrogen (1, 2 or 4 mg of oestrogen) regimens in another cycle. The results in each group were compared by the Wilcoxon matched pair test. There were no significant differences between any of the results analysed.

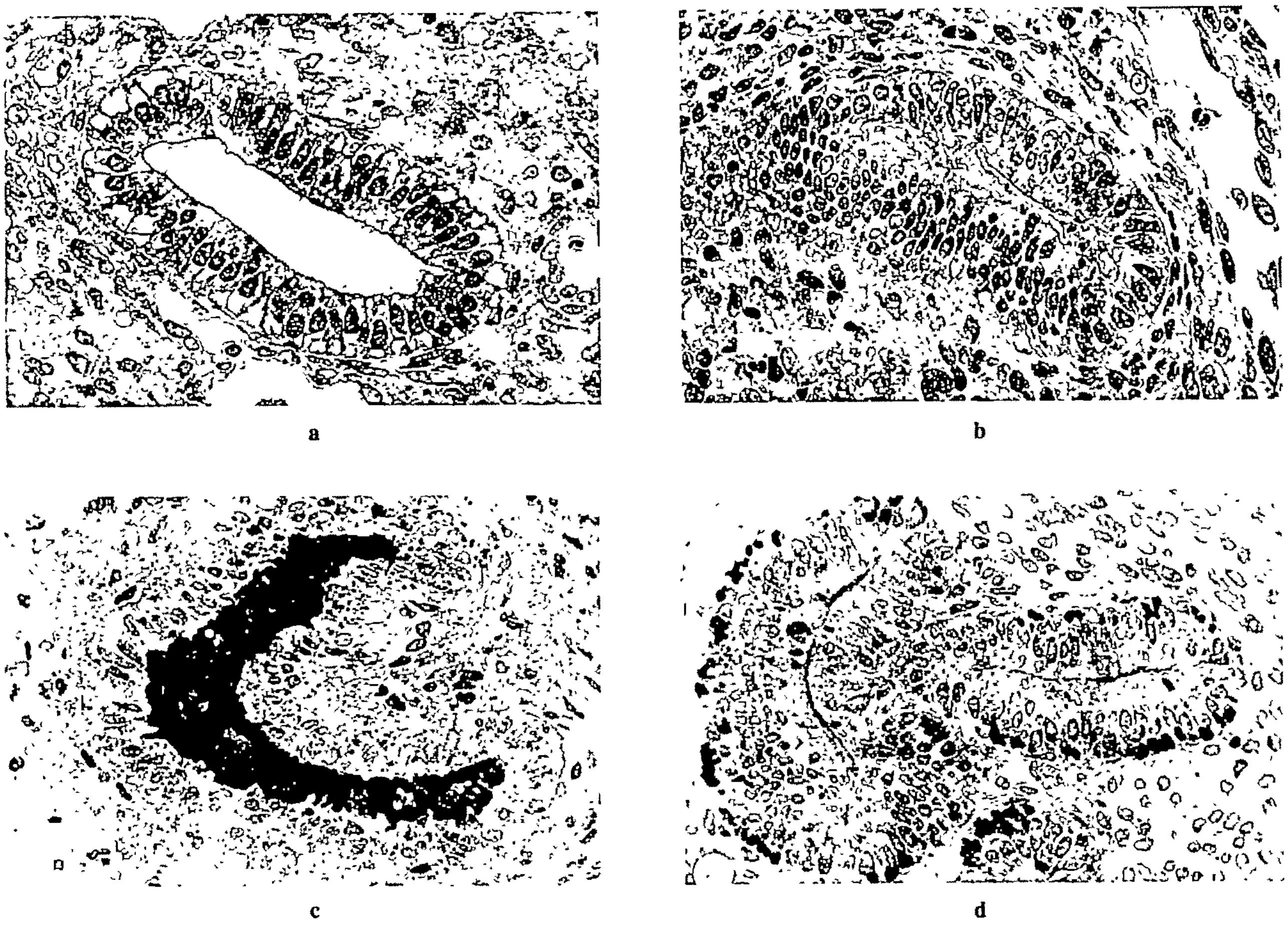

**Fig. 3.** The appearance of endometrial glands on day 19 of artificial cycles with different oestrogen dosage regimens: (a) standard regimen: note the presence of abundant sub- and supra-nuclear secretory vacuoles (magnification ×640). (b) fixed 1 mg oestrogen regimen: note the relative paucity of sub- and supra-nuclear secretory vacuoles (magnification ×640). (c) and (d), immunohistochemical staining enhanced with silver using antibody D9B1 raised against an endometrial glandular secretory glycoprotein; (c) standard regimen, intra-luminal secretion is present (magnification ×380); (d) fixed 1 mg oestrogen regimen, intra-luminal secretion is lacking (magnification ×380).

with the standard regimen, indicating that the fixed 1 mg oestrogen dose regimen results in sub-optimal priming of the endometrium. This is further supported by the results of morphometric analysis, which showed that treatment with the fixed 1 mg oestrogen regimen was associated with a significant ($P<0{\cdot}05$) reduction in the number of supra- and sub-nuclear secretory vacuoles in gland cells, and significant ($P<0{\cdot}05$) increase in the volume fraction of gland occupied by gland cells.

The results of immunohistochemical analysis similarly confirmed that the amount of secretory activity in the gland lumen in those treated with the fixed 1 mg oestrogen regimen was significantly less than those treated with the standard regimen. All these results indicate strongly that the fixed 1 mg oestrogen regimen does not produce adequate priming of the endometrium necessary for subsequent normal development.

Apart from the doses of oestrogen administered, the duration of oestrogen therapy may also have an important effect on the priming of the endometrium. Navot *et al.* (1989) studied the effect of variable durations of oestrogen priming and reported that endometrial development in artificial cycles was similar in those with priming duration of as short as 6 days to as long as 5 weeks. However, they subsequently reported that the pregnancy rate in those treated with a longer duration of oestrogen was higher than those treated with a shorter duration (Navot *et al.* 1991).

### *Endocrine profile*

It is of interest to compare the endocrine profiles achieved during the various oestrogen regimens (Fig. 1). On days 15 and 19 of the cycle, plasma oestradiol concentrations associated with the fixed 1 mg and 2 mg oestrogen regimens were similar and about 50% lower than concentrations achieved with the fixed 4 mg oestrogen regimen. The reason for the lack of difference in plasma oestrogen levels between the 1 mg and 2 mg regimens lies in the timing of administration of the oestrogen tablets. In the fixed 1 mg oestrogen regimen, each subject took a 1 mg tablet each morning; in the fixed 2 mg oestrogen regimen, each subject took a 1 mg tablet in the morning and another one in the evening; in the fixed 4 mg oestrogen regimen, each subject took a 2 mg dose of oestradiol valerate in the morning, and a further 2 mg dose in the evening. As the blood samples were all obtained in the early afternoon, the plasma oestradiol concentration, which closely reflected the morning dose of oestradiol valerate, was therefore similar in both the fixed 1 mg or 2 mg regimens, but was doubled in the fixed 4 mg regimens. The exact time at which blood samples are taken in relation to the administration of steroid hormones, and whether the steroid hormones are given in one or divided daily doses, have an important influence on the plasma steroid hormone concentrations. This is likely to account for the difference in the plasma steroid hormone concentrations in artificial cycles reported by previous investigators (Navot *et al.* 1986, 1989; Davies *et al.* 1990).

The endocrine basis for the suboptimal results produced by the fixed 1 mg oestrogen regimen may be apparent by considering the plasma oestradiol concentrations on day 29 of the cycle. In the fixed 1 mg oestrogen regimen, this represented the level just over 24 (28–30) h after the last dose of oestradiol valerate on the preceding day. The mean plasma oestradiol concentration was only 212 pmol/l, which is likely to be comparable to the plasma oestradiol concentration immediately before each daily dose of oestradiol between days 2 and 28 of the cycle in the fixed 1 mg oestrogen regimen. This value is below the reference range for the oestrogen surge (440–1380 pmol/l) and for the mid-luteal levels (220–960 pmol/l) in ovulatory cycles. On the other hand, the trough of plasma oestradiol concentrations achieved in the fixed 2 mg oestrogen regimen, as estimated from the results on day 29, is likely to be around 770 pmol/l, well within the reference ranges for both the oestrogen surge and mid-luteal levels.

It is of further interest to note that with the fixed 4 mg oestrogen dose regimen, the minimum plasma oestradiol concentration as estimated from the results on day 29 was well above the reference ranges for the oestrogen surge and mid-luteal levels, but this did not appear to have any adverse effect on endometrial development.

### *Study design*

It should be pointed out that the present study was designed to compare a standard, variable dose regimen, with three different fixed dose regimens (1 mg, 2 mg and 4 mg). Whereas we have made direct, within-subject comparison between the standard regimen and each of the three, fixed dose regimens, we have not attempted to compare the various fixed dose regimens (i.e. between-group comparisons). We feel that such a between-group comparison is inappropriate because there is significant inter-subject variability in endometrial response to steroid hormones; in addition, the number of subjects in each group is relatively small ($n = 7$). Thus it is not possible to deduce from our data whether or not there is a difference between the fixed 2 mg and 4 mg regimens; to address this would require a further study with a group of subjects receiving the fixed 2 mg regimen in one cycle and crossed-over to the fixed 4 mg regimen in another cycle.

### *Clinical relevance*

This study suggests that adequate priming of the endometrium in the artificial cycle may be achieved not only by the sequential, variable oestrogen dose regimen, but also the fixed oestrogen dose regimen. The latter is simpler and is therefore likely to replace the former in donor oocyte programmes involving artificial cycles. However, the daily dose of oestradiol valerate used should be no less than 2 mg.

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GYNAECOLOGY

# Increase in bone mass after one year of percutaneous oestradiol and testosterone implants in post-menopausal women who have previously received long-term oral oestrogens

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## ABSTRACT

**Objective** To determine the effect on the bone density of the skeleton after changing from oral oestrogen to subcutaneous oestradiol and testosterone replacement.

**Design** Prospective non-randomized single centre study.

**Subjects** Twenty women who were receiving long-term oral oestrogen replacement. Ten changed to oestradiol and testosterone implants; the remaining ten continued with oral oestrogens.

**Main outcome measures** Bone density was measured using dual photon absorptiometry at the lumbar spine and neck of femur at the start of the study and after one year.

**Results** The bone density increased significantly by 5·7% at the spine and by 5·2% at the neck of femur in those women who changed to implant therapy but remained unchanged in those women who continued with oral therapy.

**Conclusion** Subcutaneous oestradiol and testosterone implants will result in an increase in bone mass even after many years of oral oestrogen replacement therapy.

Hormone replacement therapy is effective in alleviating climacteric symptoms (Greenblatt & Studd 1977), preventing osteoporosis (Lindsay *et al.* 1976) and has been shown to reduce significantly the mortality from ischaemic heart disease and cerebrovascular accidents (Ross *et al.* 1981; Paganini-Hill 1988). Oestrogen may be given orally or parentally in the form of creams, transdermal patches or subcutaneous implants (Drife & Studd 1991). The parenteral routes have a number of advantages in that gastrointestinal side effects are avoided and by obviating the first-pass effect through the liver a physiological ratio of oestradiol to oestrone is achieved.

The hormonal profiles of women receiving oral oestrogen replacement often remain in the post-menopausal range whereas the serum oestradiol and FSH levels are within the premenopausal range following long-term hormone implants (Studd & Whitehead 1989). We have reported previously that the higher serum oestradiol levels achieved with long-term subcutaneous implants are associated with a greater bone density than found in women receiving long-term oral oestrogen replacement (Savvas *et al.* 1988). Subcutaneous hormone implants result in a substantial increase in bone density and we have demonstrated that the increase in bone density following hormonal implants correlated significantly with serum oestradiol but showed no correlation with serum testosterone (Studd *et al.* 1990). This indicates that the superiority of this mode of therapy is due to the higher oestradiol levels achieved. A number of women do not obtain satisfactory symptomatic relief with conventional oral hormonal therapy as the FSH levels remain high and the plasma oestradiol levels are inadequate. The present study was designed to investigate the effect on bone density when women change from oral oestrogen replacement therapy to subcutaneous hormone implants.

We recruited 10 women who had received oral hormone therapy for a number of years but were still troubled by climacteric symptoms and were requesting hormone replacement therapy with subcutaneous implants. These were compared with 10 women who remained on oral hormone replacement therapy.

## Subjects and methods

Twenty women receiving long-term oral oestrogen replacement were recruited for this study. Ten women (Group I) were happy to continue with oral hormone replacement but 10 (Group II) were changed to subcutaneous implants as they were complaining of problems with depression, loss of energy and loss of libido although the vasomotor symptoms were controlled.

There was no statistically significant difference in the age,

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**Table 1.** Initial hormone profiles and bone densities in 10 women receiving long-term oral hormone replacement therapy and values, after a further year of oral therapy.

| Variable | Initial | After a further year of oral therapy |
|---|---|---|
| Age (years) | 60 (50–67) | |
| Years from menopause | 8 (6–15) | |
| Duration of treatment with oral oestrogens (years) | 8 (2–14) | |
| Serum FSH (iu/l) | 40·5 (0·9–61) | 37 (25–45) |
| Serum estradiol (pmol/l | 176 (64–351) | 201 (125–448) |
| Serum testosterone (nmol/l) | | |
| Bone density (gHa/cm$^2$) | 0·85 (0·4–1·1) | 0·5 (0·4–0·6) |
| Vertebral | 0·92 (0·09) | 0·92 (0·1) |
| Femoral | 0·78 (0·08) | 0·80 (0·1) |

Results are median (range) or mean (SD) values as appropriate

number of years past the menopause, duration of treatment with oral therapy, initial hormonal profile and initial bone density between the two groups (Table 1).

The women in Group I had received oral oestrogen replacement in the form Prempak C 1·25 mg (Ayerst, 1·25 mg conjugated oestrogen daily and 150 μg norgestrel for 12 days a month) for a median of 8 years (range 2–14). The women in Group II had received Prempak C at the same dose for a similar length of time (median 5 years, range 2–18) before changing to subcutaneous hormone implants with oestradiol 75 mg and testosterone 100 mg. The implant was repeated at 6 monthly intervals.

Hormonal profiles were measured in all women at the beginning of the study and a year later which usually coincided with the visit for the third implant. Bone density measurements were performed in all women using dual photon absorptiometry at the lumbar spine and neck of femur. A Novo 22A BMC-LAB absorptiometer utilizing a Gadolinium-153 source was used. The precision was determined by repeated measurement in 10 subjects at both sites at 12 weekly intervals, giving a precision of 2·0% at the lumbar spine and 2·2% at the femoral neck.

**Table 2.** Initial hormone profiles and bone densities in 10 women receiving long-term oral hormone replacement therapy and values after a year of subcutaneous oestrogen implants

| Variable | Initial | After one year of implants |
|---|---|---|
| Age (years) | 52 (47–64) | |
| Years from the menopause | 7 (2–16) | |
| Duration of treatment with oral oestrogens (years) | 5 (2–18) | |
| Serum FSH (iu/l) | 45 (11–70) | 10 (1·6–22)* |
| Serum oestradiol (pmol/l | 164 (88–372) | 437 (312–519)* |
| Serum testosterone (nmol/l) | | |
| Bone density (gHa/cm$^2$) | 0·7 (0·4–2·2) | 2·0 (0·6–3·0)* |
| Vertebral | 0·87 (0·11) | 0·92 (0·1)** |
| Femoral | 0·76 (0·1) | 0·80 (0·12)** |

* $P<0{\cdot}01$ Mann Whitney $U$-test
** $P<0{\cdot}01$ paired $t$-test.
Results are median (range) or mean (SD) values as appropriate.

*Statistical analysis*

The changes in bone density were analysed using the paired $t$-test; the hormonal data were analysed using the Mann Whitney $U$ test.

## Results

The initial median hormonal profiles were in the post-menopausal range in both groups of women and remained in this range after a further year of oral oestrogen in Group I (Table I). In Group II (Table 2) the serum oestradiol level increased significantly from a median of 164 pmol/l (range 88–372) to 437 pmol/l (range 312–519, $P<0{\cdot}01$) and the serum FSH was reduced significantly from 45 iu/l to 10·0 iu/l ($P<0{\cdot}01$) after one year of subcutaneous hormonal therapy.

The bone density at the lumbar vertebrae and femoral neck was unchanged in the group that continued with oral oestrogen (Table 1). However, in the group that converted to implant therapy the bone density increased by 5·7% from 0·87 gHa/cm$^2$ to 0·92 gHa/cm$^2$ at the spine ($P<0{\cdot}001$). The bone density at the femoral neck increased by 5·2% from 0·76 gHa/cm$^2$ to 0·80 gHa/cm$^2$ (Table 2). The individual changes in bone density in the women in the study are illustrated in Figs 1 and 2.

## Discussion

Numerous studies have demonstrated the efficacy of oral oestrogens in the prevention of further postmenopausal bone loss (Lindsay *et al.* 1976). These studies suggest that if oestrogen therapy is started soon after the cessation of periods before significant loss of bone mass has occurred, osteoporosis can be prevented. However, the hormonal profiles of women receiving long-term oral oestrogens often remain in the post-menopausal range. This may be due to first-pass liver metabolism or poor patient compliance. Various studies have shown that up to 70% of women do not take the prescribed oestrogens at all or fail to take them on a regular basis (Ravnikar 1987; Hahn 1989). Subcutaneous implants avoid both problems and

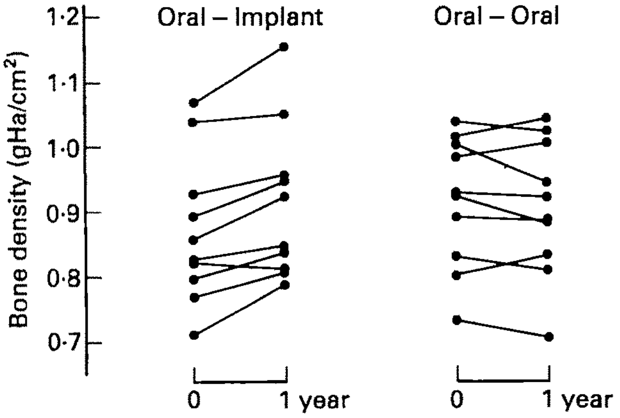

**Fig. 1.** Changes in bone density of the spine over 1 year in 10 women who continued Prempak 1·25 mg and in 10 women who changed to implants of oestradiol 75 mg and testosterone 100 mg

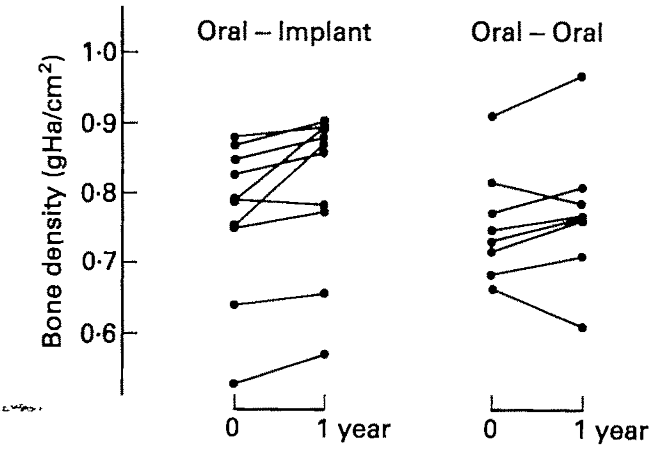

**Fig. 2.** Changes in bone density of the proximal femur over 1 year in 10 women who continued Prempak 1·25 mg and in 10 women who changed to implants of oestradiol 75 mg and testosterone 100 mg.

achieve a significantly higher serum oestradiol level and lower FSH level.

The two groups in this study were self-selected in that those women who were changed to implant therapy were still experiencing some climacteric symptoms with oral therapy and this may have been due to poor patient compliance. The increase in bone density seen following one year of implants may thus be due to avoiding patient non-compliance. However, there was no significant difference in the initial serum oestradiol and FSH levels between the two groups suggesting that they were well matched in terms of compliance.

We have previously demonstrated that the increase in bone mass seen with subcutaneous oestradiol and testosterone implants correlates significantly with the serum oestradiol level (Studd *et al.* 1990). Our findings suggest that the serum oestradiol levels achieved with oral hormone replacement therapy at the conventional dose may be sub-optimal and that subcutaneous oestradiol and testosterone implants will lead to an increase in bone density by further increasing the serum oestradiol in women who have received long-term oral hormone replacement therapy. The levels achieved with oral therapy in this study are of the same order as those seen in other studies of oral hormone replacement therapy (Powers *et al.* 1985). This supports the suggestion that the improved bone density seen in postmenopausal women receiving implants is due to the rise in serum oestradiol levels. This benefit is not transient as cross-sectional studies have indicated a prolonged improvement in bone density with up to 14 years of hormone implants (Garnett *et al.* 1991). Studies from this unit indicate that addition of testosterone has no significant added effect on bone density (Studd *et al.* 1990).

The concept of increase in bone density following hormone therapy is established in other conditions characterized by a deficiency of sex steroids. Treasure *et al.* (1987) have demonstrated that bone loss associated with anorexia nervosa is reversed when weight is regained and menstruation returns. Osteoporosis seen in men with hyperprolactinaemic hypogonadism is also reversed following either medical or surgical treatment that results in normal circulating levels of sex steroids (Greenspan *et al.* 1986; Finkelstein *et al.* 1989). Loss of vertebral bone mass in amenorrhoeic women athletes is reversed after the resumption of menstruation (Drinkwater *et al.* 1986), and bone loss following the down regulation of the pituitary gonadotrophin secretion with GnRH use is regained after stopping treatment (Matta *et al.* 1988).

This study supports the view that adequate oestrogen therapy which returns serum oestradiol levels to premenopausal values will also reverse postmenopausal bone loss. This suggestion has currently little support because most studies have investigated the effect of oral oestrogen replacement and the consensus of these studies is that such therapy can only prevent further bone loss and cannot reverse significantly any bone loss that may already have occurred. However, Horsman *et al.* (1983) have demonstrated that the skeletal response to oral ethinyloestradiol is dose dependent with 15 µg daily preventing bone loss whereas 25 µg resulted in significant increase in bone mass. Epidemiological studies confirm the value of oral oestrogen replacement in the prevention of fractures with 5-year use being associated with a 50% reduction in overall fracture rates (Mazess *et al.* 1989). Vertebral, forearm and rib fractures are convincingly reduced but there is less protection against the more important femoral neck fractures.

Melton *et al.* (1986) have shown that the risk of fracture is closely related to bone density. It may be that the greater increase in bone density seen with hormone implants is associated with a greater protective effect on fracture incidence, although this will only be confirmed by epidemiological studies and prospective histological studies of bone morphology.

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REPRODUCTIVE SCIENCE

# Plasma endothelin, atrial natriuretic peptide (ANP) and uterine and umbilical artery flow velocity waveforms in hypertensive pregnancies

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**ABSTRACT**

**Objective** To investigate the relation between concentrations of endothelin and atrial natriuretic peptide (ANP) in maternal plasma and vasospasm in the uterine and umbilical arteries as detected by duplex pulsed colour Doppler ultrasonography in hypertensive pregnancies.

**Design** An observational study.

**Subjects** 32 women admitted consecutively to hospital with pregnancy induced hypertension (seven without proteinuria and 25 with proteinuria) and 78 healthy pregnant women examined at 28–40 weeks gestation.

**Main outcome measures** Systolic/diastolic (S/D) ratio in flow velocity waveforms (FVWs) and plasma concentrations of endothelin and ANP in the 32 women with pregnancy induced hypertension; plasma concentrations of endothelin and ANP in 78 healthy pregnant women (controls).

**Results** Pathological FVWs suggesting vasospasm in the uterine or umbilical artery, or both arteries, were found in 12 women with hypertension. Plasma ANP was significantly higher ($P = 0{\cdot}03$) in the women with hypertension and pathological FVWs (median 23·0, range 10·1–52·8 pmol/l) than in those with hypertension and normal FVWs, (median 13·8, range 5·3–42·3 pmol/l) but corresponding plasma endothelin levels did not show any significant difference (median 1·63, range 0·51–3·33 pmol/l and median 1·38, range 0·51–3·51 pmol/l, respectively).

**Conclusion** Local release of endothelin from the vascular endothelium is thought to cause vasospasm in pregnancy induced hypertension but this does not seem to increase the concentration of endothelin in the maternal peripheral plasma, probably because of its rapid disappearance from the blood circulation. As ANP dilates the blood vessels, the increase of its release in hypertensive pregnancies may be a compensatory mechanism against vasospasm.

Endothelin is a 21 amino acid peptide released by the vascular endothelium (Yanagisawa *et al.* 1988). Intravenous infusion of synthetic endothelin-1 causes a long lasting elevation of blood pressure in the rat (Yokokawa *et al.* 1989), which indicates that this peptide is a potent vasoconstrictor. The underlying mechanism is an increase in intracellular calcium, as has been demonstrated in cultured smooth muscle cells (Marsden *et al.* 1989). Elevated plasma endothelin has been reported in non-pregnant subjects with severe hypertension (Kohno *et al.* 1990) and in pregnant women with pre-eclampsia (Taylor *et al.* 1990; Dekker *et al.* 1991). Endothelin may, therefore, be an important vasoconstrictor in the pathogenesis of hypertension and elevated plasma endothelin may be a marker of disturbed endothelial function as a result of pre-eclampsia (Roberts *et al.* 1989).

Atrial natriuretic peptide (ANP) is synthesized in the atrial myocytes and released as a result of increased intra-atrial pressure or stretching (Ruskoaho *et al.* 1987). Pressor hormones such as vasopressin (Ruskoaho *et al.* 1987) and endothelin (Hu *et al.* 1988; Stasch *et al.* 1989; Mäntymaa *et al.* 1990) also stimulate its release. The vascular smooth muscle and kidneys are the main targets of ANP, which relaxes the vascular tonus and reduces blood pressure. Like endothelin, plasma ANP levels are increased in pre-eclampsia (Thomsen *et al.* 1987; Otsuki *et al.* 1987). Thus, both endothelin and ANP may regulate vascular tone in pre-eclampsia.

Information on increased vascular resistance in the uterine and umbilical arteries can be obtained by demonstrating pathological blood flow velocity waveforms (FVWs) with Doppler ultrasound (Gudmundsson & Marsal 1988a). We have investi-

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gated the relation between haemodynamic findings and plasma levels of endothelin and ANP in hypertensive and pre-eclamptic pregnancies.

## Subjects and methods

The investigation was approved by the Oulu University ethics committee. Altogether, 32 consecutive women with singleton pregnancies and hypertension (≥140/90 mmHg) who were admitted to the hospital were enrolled. Seven primigravid women, including three on labetalol treatment, developed hypertension without proteinuria. The mean (SEM) systolic and diastolic blood pressures in these women on admission were 154 (3·5) and 96 (2·5) mmHg, respectively. The other 25 women developed proteinuria in addition to hypertension between 26 and 38 weeks gestation. Sixteen of the women with proteinuria were primigravid and seven of the remaining nine were known to have had hypertension and proteinuria in an earlier pregnancy. The mean (SEM) systolic blood pressure in the proteinuric group on admission was 154 (2·7) mmHg, the mean (SEM) diastolic blood pressure was 95 (1·5) mmHg and the mean (SEM) urinary protein concentration was 1·97 (0·52) g/l. Twelve of the 25 women with proteinuria had already commenced antihypertensive treatment with labetalol, 100 mg three times daily, but the blood pressure remained >160/100 mmHg in five of them and eclampsia developed in two of these five women.

The first examination was performed between 28 and 40 weeks gestation and the tests were repeated weekly if the patient remained in hospital. Uterine and umbilical artery FVWs were recorded by duplex pulsed colour Doppler ultrasound (Toshiba DSSA-270A, 3.74 MHz sector probe). A pathological systolic/diastolic (S/D) ratio in the FVWs for the uterine and umbilical arteries was defined as the mean +2SD of values in uncomplicated pregnancies at a corresponding stage of gestation (Gudmundsson & Marsal 1988b).

A 10 ml blood sample was collected into a vacuum tube containing EDTA (1·5 mg/ml of blood) at the time of Doppler examination. Blood samples were also taken from a control group of 78 healthy women enrolled from the outpatient clinic between 28 and 40 weeks gestation. The age, gestational age and parity of the controls were similar to the hypertensive group and their blood pressure had not exceeded 140/90 mmHg at any routine examinations. One blood sample was taken from each subject. The plasma was separated out immediately by centrifugation and stored at −20° C until analysed.

The 2 ml plasma samples for radioimmunoassay were extracted with Sep-Pak $C_{18}$ cartridges (Waters Ltd., California, USA) as described in the manufacturer's instructions and incubated in duplicates of 200 μl for 24 h 5°C with 100 μl of '9–50' rabbit antiserum for the ANP assay (Vuolteenaho *et al.* 1985) and with rabbit antiserum no. 6901 (Penisular Laboratories, Ltd., Heidelberg, Germany) for the endothelin assay. Approximately 10 000 cpm of $^{125}$I-labelled rat ANP 1–28 or endothelin-1 was then added in 100 μl of RIA buffer and the incubation was continued for another 24 h at 5°C. The bound and free fractions were separated by precipitation with sheep anti-rabbit gammaglobulin serum in the presence of 8% polyethylene glycol 6000. The sensitivities of the ANP and endothelin assays were 0·65 fmol/tube and 0·4 fmol/tube, respectively. The intra-assay and inter-assay coefficients of variation were <10% and <15%, respectively, in both assays.

Mann Whitney *U* test, Student's *t* test and $\chi^2$ test were used for comparisons between the groups as appropriate.

## Results

No significant difference in plasma endothelin concentration was found between the healthy and hypertensive pregnant women (first visit data only) but the ANP concentration was significantly higher ($P = 0{\cdot}0001$) in the women with hypertension and proteinuria than in the healthy pregnant controls (Table I).

There was no significant difference in the concentrations of ANP and endothelin between the 15 hypertensive women receiving labetalol treatment and the 17 women not receiving labetalol. No significant correlations were found between systolic or diastolic blood pressures and plasma endothelin or ANP values, or between endothelin and ANP values.

Pathological FVWs were observed in 12 women, all of whom had hypertension with proteinuria. In 11 of these women the uterine arterial S/D ratio was 2·8 to 5·3, suggesting vasospasm, and in the other woman the uterine arterial S/D ratio was normal but the umbilical artery S/D ratio was elevated at 4·3. In 9 of the 11 pregnancies with a pathological S/D ratio in the uterine artery, the umbilical artery S/D ratio was also elevated, from 2·5 to 5·2, and absent diastolic flow in the umbilical artery was observed in one of them. Observations on the groups with normal and pathological FVW findings are compared in Table 2. Three of the five women with persistent blood pressure >160/100 mmHg, including the two women with eclampsia, had pathological uterine arterial FVWs, as did nine out of 12 women who gave birth to an infant with intrauterine growth retardation.

The distribution of endothelin and ANP values in women with hypertension is given in relation to the FVW findings in Fig. 1 and summarized in Table 2. The concentration of endo-

**Table 1.** Median (range) concentrations of endothelin and atrial natriuretic peptide (ANP) in maternal plasma in uncomplicated pregnancy, pregnancy induced hypertension and pre-eclampsia.

| Group | *n* | Endothelin (pmol) | ANP (pmol) |
|---|---|---|---|
| Uncomplicated pregnancy | 78 | 1·81 (0·69–4·0) | 5·86 (0·66–23·9) |
| Pregnancy-induced hypertension | | | |
| Without proteinuria | 7 | 0·93 (0·51–1·96) | 10·6 (6·7–20·6) |
| With proteinuria | 25 | 1·53 (0·51–3·17) | 17·1 (5·3–52·6)* |

*$P = 0{\cdot}0001$, compared with the uncomplicated pregnancies (Mann Whitney *U* test).

**Table 2.** Comparison of observation in hypertensive pregnancies with normal and pathological uterine and umbilical artery flow velocity waveform (FVW) characteristics at the first examination.

| | Normal ($n$ = 20) | Pathological FWV ($n$ = 12) |
|---|---|---|
| Gestational age (weeks) | 37·2 (0·47) | 35·2 (1·1) |
| Systolic blood pressure (mmHg) | 154 (2·9) | 156 (3·4) |
| Diastolic blood pressure (mmHG) | 95 (1·7) | 96 (1·9) |
| Uterine artery S/D ratio | 2·3 (0·16) | 3·6 (0·36)$^a$ |
| Umbilical artery S/D ratio | 2·4 (0·06) | 3·2 (0·03)$^b$ |
| Endothelin (pmol/l) | 1·38 (0·51–3·5) | 1·63 (0·51–3·3) |
| ANP (pmol/l) | 13·8 (5 3–42·3) | 23·0 (10·1–52·8)$^c$ |
| Delivery before 37 weeks | — — | 5 (42%)$^d$ |
| Induction of labour | 12 (60%) | 10 (83%) |
| Caesarean section | 3 (15%) | 7 (58%)$^e$ |
| Intrauterine growth retardation | 3 (15%) | 9 (75%)$^f$ |

Values are mean (SEM), median (range) or (%), as appropriate. Comparison between normal and pathological FVWs: $^a$: $P$ = 0·001; $^b$: $P$ = 0·03 (Student's $t$ test); $^c$: $P$ = 0·03 (Mann Whitney $U$ test); $^d$: $P$ = 0·002; $^e$: $P$ = 0·01; $^f$: $P$ = 0.002 ($\chi^2$ test).

thelin was similar in women with normal and pathological FVW findings, but the concentration of ANP was significantly higher in the hypertensive women with vasospasm than in those with normal flow ($P$ = 0·03).

FVW characteristics and plasma endothelin and ANP levels were recorded for at least 2 weeks in 17 hypertensive women, but no parallel changes in plasma levels of ANP or endothelin and the uterine arterial S/D ratio were found.

## Discussion

The range of plasma endothelin concentrations in normal and hypertensive pregnancies which we observed is in accordance with previous findings (Taylor *et al.* 1990; Dekker *et al.* 1991), and is so low that circulating endothelin probably does not have any general effect on the vasculature. A concentration of endothelin of approximately 60 pmol/l was found to elicit a contractile response *in vitro* (Yanagisawa *et al.* 1988).

We were not able to demonstrate any significant increase in the concentration of plasma endothelin in pregnant women with hypertension although Dekker *et al.* (1991) have recently reported elevated plasma endothelin levels in a few cases with severe pre-eclampsia or HELLP syndrome. Our finding that hypertension in pregnancy is not commonly associated with increased plasma endothelin levels may be due to the rapid disappearance of endothelin from the blood circulation, especially the pulmonary circulation (De Nucci *et al.* 1988). Disturbed kidney (Tomita *et al.* 1989) or liver (Dekker *et al.* 1991) function may explain the increased plasma endothelin level in severe pre-eclampsia.

Our findings do not exclude the possibility that in hypertensive pregnancies endothelin is released locally in the vascular endothelium to cause vasospasm without any increase in concentration in peripheral plasma. Increased endothelin levels in umbilical artery blood collected at caesarean section have been reported in cases with absent end-diastolic flow in the umbilical artery detected by ultrasound (Hartikainen-Sorri *et al.* 1991). In the four cases reported, the plasma endothelin level in the maternal plasma was normal, showing that local production of endothelin may be increased without any effect on the concentration in the systemic circulation.

Serum from pregnant women with pre-eclampsia was found to suppress endothelin production by term umbilical cord endothelial cells *in vitro* (Branch *et al.* 1991), suggesting that there is a homeostatic mechanisms regulating endothelin production in pre-eclampsia. ANP may be a factor in such a homeostatic mechanism as it was found to reduce both basal and thrombin-stimulated production of endothelin by cultured human endothelial cells *in vitro* (Saijonmaa *et al.* 1990). The lowest inhibitory concentration of ANP was approximately 30 pmol/l, which is within the range of plasma concentrations we found in hypertension and proteinuria. Thus, the inhibitory effect of ANP on endothelin release may also be relevant *in vivo*.

Plasma ANP increases during normal pregnancy (Milsom *et al.* 1988), a trend which has been explained by an approximately 30% increase in circulating blood volume which stimulates its release. The level of plasma volume expansion is diminished in pre-eclampsia which does not explain the further increase in ANP concentration in this condition. However, the vasoconstriction that occurs is believed to increase the local volume load in the cardiac atria, which would explain the

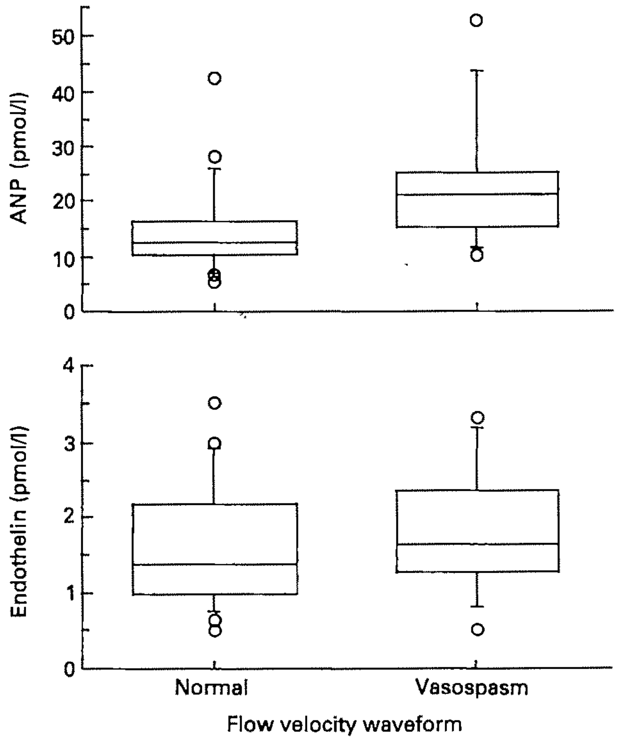

**Fig. 1.** Concentrations of endothelin and atrial natriuretic peptide (ANP) in hypertensive pregnancies with or without pathological Doppler flow velocity waveforms. The lower and upper bars represent the 10th and 90th centiles, respectively, and the interquartile range is indicated by the box, the median value being the horizontal line in the box. The ANP values were significantly higher ($P$ = 0·03) in cases with vasospasm.

increased release of ANP into the circulation (Miyamoto *et al.* 1988). In our study, vasospasm in the uterine arteries was associated with increased plasma ANP levels. It is possible that the increased ANP release in hypertensive pregnancies represents a mechanism for counteracting the effect of vasopressors, for there is experimental evidence that ANP selectively increases placental blood flow in the rat (Chemtob *et al.* 1989).

We conclude that plasma endothelin does not seem to be a suitable marker for detecting hypertensive pregnancies with vasospasm, although our findings do not exclude a possible pathophysiological role of endothelin in this condition. There was, however, an association between the plasma ANP level and changes in vascular haemodynamics in hypertensive pregnancies; this was related to the severity of the hypertensive disease. Thus ANP determinations may be beneficial for detecting cases which entail a risk of vasospasm.

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REPRODUCTIVE SCIENCE

# Distribution of renin-containing cells in the developing human kidney: an immunocytochemical study

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ABSTRACT

**Objective** To characterize the pattern of renin containing cells (RCC) within the human kidney between 20 weeks of gestation and 6 months of postnatal life.

**Design** Descriptive study using paraffin-embedded blocks of kidney stored following postmortem examination.

**Methods** Sections of kidney were stained immunocytochemically using an antibody to human renin; the proportion of RCC within each of three zones (superficial, middle and deep) of the cortex, and their anatomical relation to individual glomeruli were determined. The cases were divided into five groups for analysis to gestational or postnatal age.

**Results** Fetal RCC were usually at the vascular pole of the most mature glomeruli within the deeper areas of the cortex and were occasionally located within glomeruli. This distribution persisted until birth, even when the kidney was histologically mature. By contrast there were fewer RCC in neonatal and infant kidneys and, as in adult kidneys, these were located predominantly in the superficial cortex.

**Conclusion** The change in RCC distribution around the time of normal birth may relate to the transition to independent renal function. The location and density of RCC during fetal life may influence renal perfusion and amniotic fluid production.

The clinical importance of a normal amniotic fluid volume during pregnancy is well recognized (Manning *et al.* 1981), and conversely, oligohydramnios is a marker of adverse perinatal outcome related to intrauterine growth retardation (Bustide *et al.* 1986). Furthermore, the fetal kidney is the main source of amniotic fluid as pregnancy advances (Campbell *et al.* 1973). Thus, knowledge of the mechanisms which govern fetal renal blood flow and urine production may contribute to a better understanding of the pathophysiology of oligohydramnios and intrauterine growth retardation.

Renin release generates angiotensin II within the kidney (Mendelsohn 1982). This local (paracrine) action of renin within the fetal kidney may influence renal blood flow and urine output (Robillard & Nakamura 1988). This phenomenon is likely to be governed by the location of the renin-containing cells within the kidney. To date the study of these cells in the human kidney has been confined to early pregnancy (Phat *et al.* 1981; Celio *et al.* 1985). In this paper we report the distribution of renin-containing cells within the human kidney in the latter part of pregnancy, between 20 weeks gestation and 6 months of postnatal life, with special reference to the changes around the perinatal period when the kidney assumes independent function.

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## Materials and methods

A total of 40 human kidneys were obtained at post-mortem examinations. Twenty-one were from miscarriages or legal abortions, and from stillbirths between 20 and 42 weeks gestation, while the remaining 19 were from infants born at term, and who subsequently lived for periods ranging from 5 h to 6 months; in 13 of these infants, death was ascribed to the sudden infant death syndrome. Other causes of death were bronchopneumonia, meconium aspiration syndrome, perinatal asphyxia, congenital malformations and endocardial fibroelastosis. The kidneys were all histologically normal and all specimens from either the miscarriage or stillbirth categories demonstrated histological features which were in keeping with the stated gestational age. Apart from one, all specimens obtained from stillbirths or infants after 40 weeks gestation showed full maturation of the kidney.

*Immunocytochemistry*

Standard 4 μm sections were cut from formalin-fixed paraffin-embedded tissue. A section of the entire kidney was mounted on each slide. The primary antibody was a rabbit antiserum raised to purified human renin, whose staining specificities have been characterized previously (Lindop *et al.* 1987). This was applied to the sections (diluted to 1/1000) and incubated (along with negative controls) overnight at 4°C. Antibody binding was demonstrated by a standard peroxidase anti-peroxidase (PAP) technique, using a diaminobenzidine reaction as described previously (Lindop *et al.* 1983). Following this, the sections were counterstained using periodic acid-Schiff; adjacent sections were stained with haematoxylin and eosin, and Masson's trichome.

*Mapping of renin distribution*

The distribution of renin-containing cells within the renal cortex was assessed by constructing maps of rectangular areas of cortex (excluding colums of Bertin). The observer was ignorant of the clinical information. These areas were scanned in a battlement fashion by plotting the position of each glomerulus, artery, arteriole and renin-containing cell on graph paper; one square on the paper corresponded to one high-power microscope field (×40) as described previously (Graham *et al.* 1990). On these maps the width of the renal cortex was arbitrarily divided into three horizontal zones of equal depth. The number of renin-containing cells in each zone was counted and expressed as a percentage of the total number in the section as a whole. It was thus possible to assess which proportion of these cells lay in the superficial, middle or deepest zones of the renal cortex. In addition, we counted the numbers of renin-containing cells which were associated with a juxtaglomerular apparatus, or were related to a more distant artery or arteriole. The cases were divided into five groups according to gestational or postnatal age at the time of death, and subsequently categorized according to which zone contained the most renin-containing cells in each kidney.

## Results

*Anatomy of renin-containing cells*

In all 40 kidney specimens, irrespective of either gestational or postnatal age, the majority of renin-containing cells were located at the vascular poles of glomeruli, corresponding to the juxtaglomerular apparatus. Typically, a small number of cells, usually no more than 3–4 per glomerulus, could be identified by brown granular cytoplasmic staining (Fig. 1). On average there appeared to be more renin-containing cells in the juxtaglomerular apparatus in fetal than in neonatal or infant kidneys.

Fetal kidneys contained glomeruli of varying degrees of maturity. Renin-containing cells were found most often at the vascular pole of the most mature glomeruli; these were predominantly within the deeper areas of the cortex. However, there were also smaller numbers of these cells at the vascular

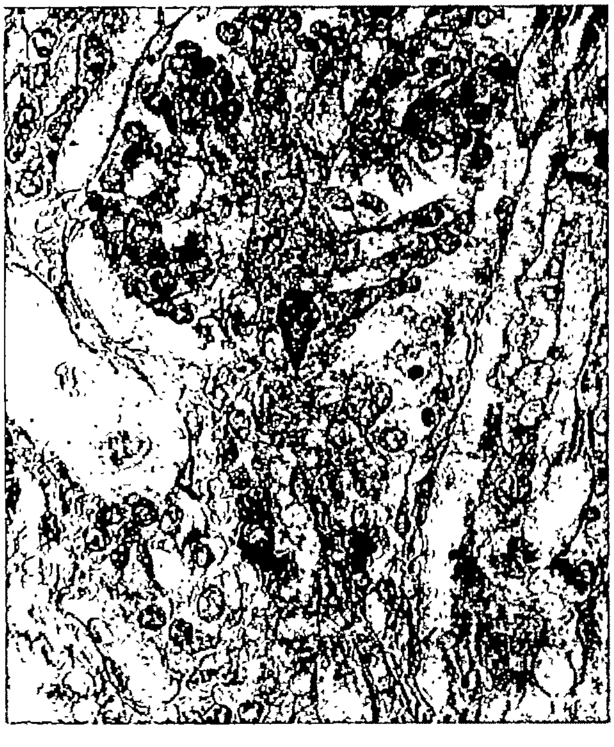

**Fig. 1.** Fetal kidney: juxtaglomerular apparatus demonstrating three renin-containing cells, two of which are in the afferent arteriole

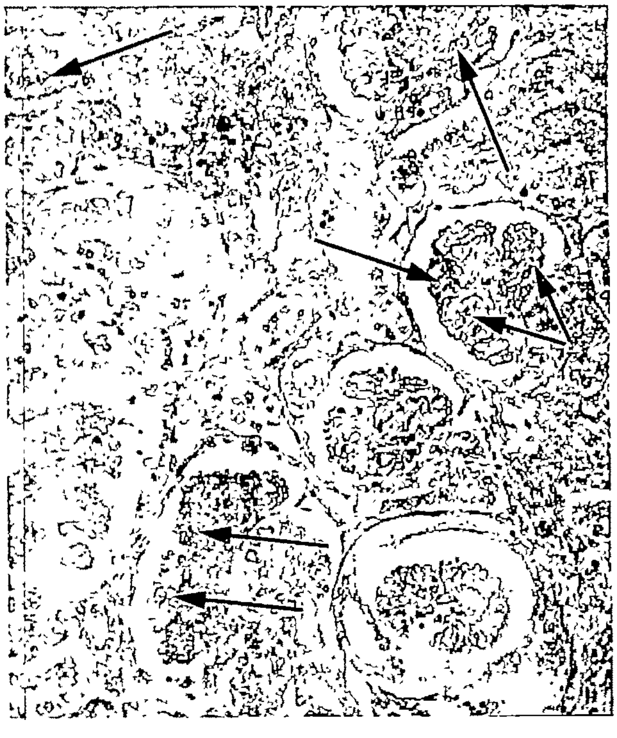

**Fig. 2.** Intraglomerular renin-containing cells (RCC) in a fetal kidney. The glomeruli are immature and the RCC are in mesangial areas (arrows).

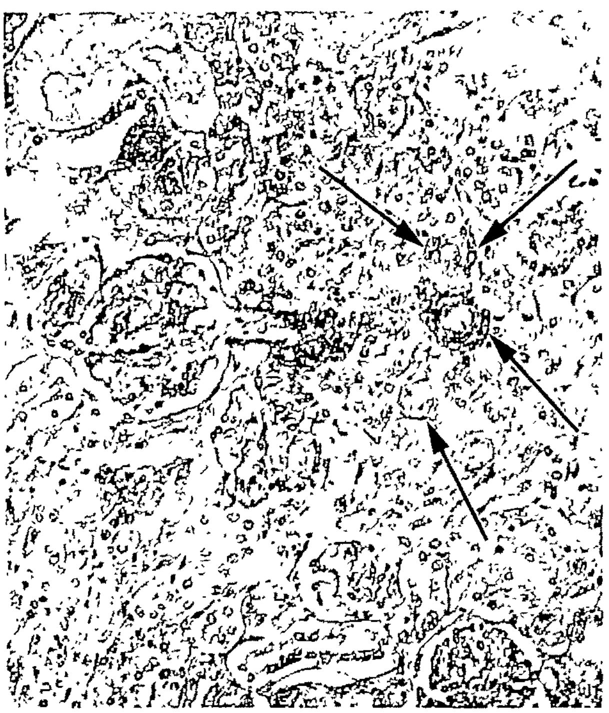

**Fig. 3.** Fetal kidney: renin-containing cells at the juxtaglomerular apparatus and on the outer aspect of arterioles (arrows).

poles of glomeruli in the more immature superficial parts of the cortex. In fetal kidneys renin-containing cells were occasionally observed within mesangial areas of less mature glomeruli in the superficial zone of the cortex (Fig. 2). These kidneys had a high total count of renin-containing cells.

All glomeruli in the neonatal and infant kidneys were mature. No intraglomerular renin was seen in either the neonatal or infant kidneys. In all kidneys some renin-containing cells were present outwith the juxta-glomerular apparatus in the walls of small arteries and arterioles distant from glomeruli (Fig. 3). The proportion of renin-containing cells (14–20% per specimen) associated with these vessels did not differ between the age groups shown in Table 1.

*Zonal distribution of renin-containing cells*

Before birth, the majority of renin-containing cells were located in the inner zone of the cortex, whereas after birth this distribution was reversed. Examples showing the distribution of renin-positive juxtaglomerular apparatus within the renal cortex of fetal and neonatal kidneys are shown in Figs 4 and 5. Table 1 shows the number of specimens within each age group in which the majority of renin-containing cells was located in the superficial, middle, or deep thirds of the renal cortex, respectively, though in most groups the occasional specimen had a different distribution of renin-containing cells. Combining these data into two larger groups (fetal and infant) demonstrates that this change in the distribution of renin-containing cells is highly significant ($\chi^2 = 17{\cdot}8$, 2 df, $P<0{\cdot}001$).

**Table 1.** The zone of the renal cortex which contained most renin-containing cells (RCC) in relation to gestational postnatal age.

| | | No. of cases with majority of RCC in | | |
|---|---|---|---|---|
| Age group of cases | *n* | Inner zone | Middle zone | Outer zone |
| Gestational age (weeks) | | | | |
| 20–30 | 10 | 6 | 3 | 1 |
| 31–38 | 6 | 4 | 1 | 1 |
| 39–42 | 5 | 1* | 1* | 1 |
| Postnatal age (weeks) | | | | |
| 1–8 | 9 | 2 | 0 | 7 |
| 9–26 | 10 | 0 | 1 | 9 |

*In two additional cases the middle and inner zone proportions of RCC were equal

## Discussion

This study demonstrates the presence of renin-containing cells within the anatomically normal fetal and early infant human kidney. Although some of our cases were clinically abnormal, our data suggest that a physiological change towards a more adult distribution pattern of renin-containing cells occurs around the time of birth. Since local renin release has been shown to generate angiotensin II within the kidney (Mendelsohn 1982), the position of the renin-containing cells in the renal vascular tree could influence arterial tone and therefore the distribution of intra-renal blood flow.

### *Developmental anatomy*

Renin-containing cells were predominantly located in the

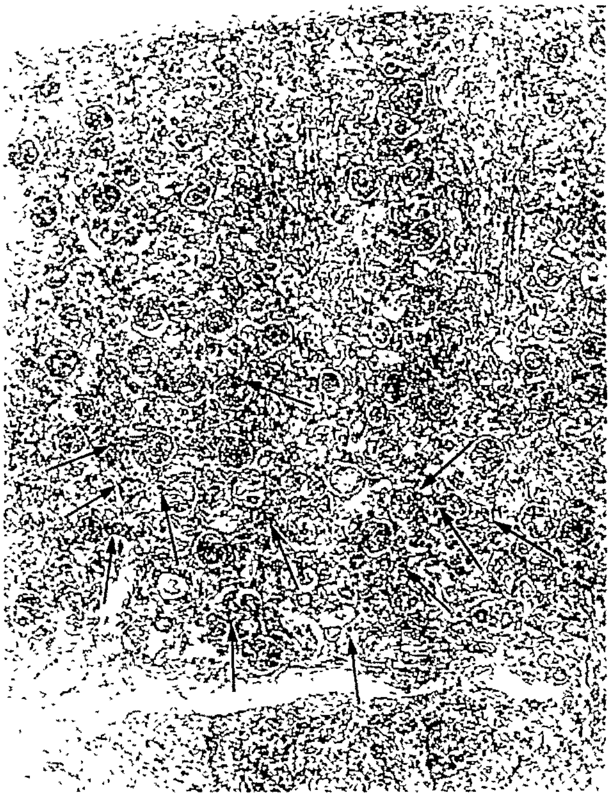

**Fig. 4.** A low-power photomicrograph of a fetal kidney showing the full thickness of the renal cortex (36 weeks of gestation); showing renin-positive JGAs (arrows) mainly in the juxtamedullary renal cortex.

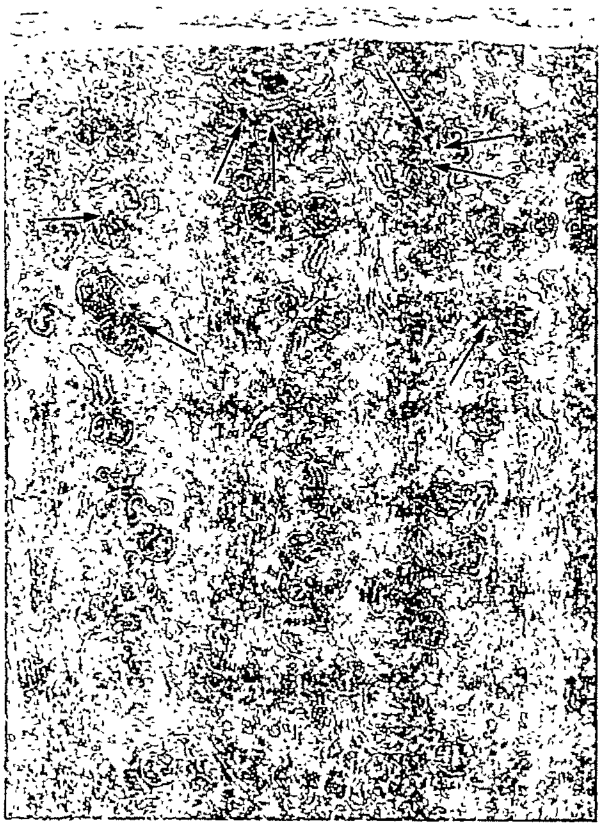

**Fig. 5.** A similar photomicrograph of a neonatal kidney shows less immunostainable renin; most of the renin-positive JGAs are now in the juxtamedullary renal cortex.

juxtaglomerular apparatus at the vascular poles of glomeruli in the walls of afferent and sometimes efferent arterioles. Smaller numbers were also present within the walls of arteries and arterioles distant from the glomerulus. In our study the largest vessels which contained renin-containing cells in the fetal kidneys were interlobular arteries, although in earlier fetal life (Celio *et al.* 1985) as in more primitive vertebrates (Sokabe 1974), renin-containing cells may be found in more proximal vessels. The extraglomular renin-containing cells may act during fetal life to modify renovascular resistance and thus influence intra–renal blood flow.

A curious additional finding was the demonstration of occasional renin-containing cells within glomeruli of some fetal kidneys. Using traditional stains, Ljunquist & Wagermark (1966) noted granular cells similar to those of the juxtaglomerular apparatus within fetal glomeruli. More recently an immunocytochemical study found mesangial renin-containing cells only during early fetal development (Celio *et al.* 1985). In glomeruli of adult kidneys, mesangial cells transform into renin-containing cells only in pathological conditions associated with chronic stimulation of the renin angiotensin system; these include Bartter's and pseudo-Bartter's syndrome (Christensen *et al.* 1989), in sclerosed glomeruli from diseased kidneys (Graham & Lindop 1988; Peh & Lindop 1991), and in experimental Addison's disease (Dunihue & Boldosser 1963). In our study, intraglomerular renin-containing cells were only within immature glomeruli in kidneys which appeared to have many of these cells. Intraglomerular renin-containing cells might therefore indicate abnormal stimulation of the fetal renin-angiotensin system in these cases; this could have adverse effects in the circulation, particularly within the placenta (Glance *et al.* 1984; McQueen *et al.* 1990).

### *Zonal distribution of renin-containing cells*

In the adult human kidney (Gardiner & Lindop 1985) and in animals (Brown *et al.* 1965) there is a gradient of renin-containing cells within the renal cortex with most cells in the superficial juxtaglomerular apparatus. This gradient is more marked in some species than in others (Wurfer *et al.* 1988). We have demonstrated a similar gradient in the human infant. However, it is also apparent from our data and from previous animal studies (Friedberg 1964; Gomez *et al.* 1986) that during fetal life the pattern of renin-containing cells is usually the reverse of the adult distribution, with these cells predominantly located in deeper parts of the cortex. This distribution persists despite histological maturation of the entire depth of cortex. This implies that the different location of renin-containing cells during fetal life is unlikely to be due to zonal maturation of the kidney. The predominance of renin-containing cells in the deep zones of the cortex is the more remarkable because the superficial renal cortex contains more glomeruli than the deep cortex (Kelly *et al.* 1990).

A reversal of this distribution usually occurs at, or shortly after, birth at term. During this time superficial glomeruli acquire renin-containing cells, whilst they are lost from juxtamedullary glomeruli. This phenomenon has been described previously in rodents by mapping the changes in renal distribution of renin (Gomez *et al.* 1986) and of renin mRNA with gestational age (Gomez *et al.* 1989; Jones *et al.* 1990); however as far as we know it has not been demonstrated in the developing human kidney.

### *Clinical implications*

A similar preponderance of renin-containing cells within the deep cortex of adult kidneys which were ischaemic due to renovascular disease suggests that renal ischaemia may influence the distribution within the kidney (Graham *et al.* 1990; Graham & Lindop 1990), and in some cases, induce a 'reversal' to a more fetal pattern. Thus both the number and the pattern of renin-containing cells within the fetal renal cortex may be caused by the low renal blood flow which characterizes fetal life (Robillard & Nakamura 1988). Local activity of renin-containing cells in the juxtamedullary juxtaglomerular apparatus would predispose to low blood flow through the fetal renal medulla and diminish sodium-retaining capacity *in utero*.

The fetal environment is characterized by a low oxygen tension (Soothill *et al.* 1986) and hypoxia probably stimulates the renin-angiotensin system both directly (Robillard *et al.* 1981; Jelinek *et al.* 1986) and perhaps indirectly by causing a fall in renal blood flow (Robillard *et al.* 1981). The abrupt rise in arterial $P0_2$ which occurs at birth may therefore be one of the stimuli for the fall in number and for the change in distribution of renal renin-containing cells which we describe. Furthermore, the fall in total numbers of these cells and their shift to the superficial cortical juxtaglomerular apparatus would be expected to have a permissive effect for an increase in renal blood flow, a prerequisite for independent renal function. The fall in numbers of renin-containing cells in the juxtamedullary juxtaglomerular apparatus should increase blood flow through the renal medulla, thereby increasing the capacity for sodium retention which occurs at the time of birth.

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## CASE REPORTS

# Ascending placentofetal infection caused by cytomegalovirus

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## Case report

A female infant, weighing 980 g was born by caesarean section at 27 weeks gestation and 27 days after prelabour rupture of membranes. She was well at birth, and was fed breast-milk from several donors beginning on day 4. Red blood cell transfusion pretreated with a filter to remove donor leukocytes was administered on day 13 for progressive anaemia due to immaturity. By day 43, the infant exhibited progressive respiratory failure and required ventilation. The chest x-ray revealed diffuse interstitial infiltration suggestive of interstitial pneumonia. Cytomegalovirus had been isolated from the infant's pharynx on day 36, and was obtained from her tracheal aspirates on day 68. Accordingly we administered ganciclovir (10 mg/kg/day) for 2 weeks. Although the respiratory status improved, there was residual chronic lung disease.

To determine the route of cytomegalovirus (CMV) transmission, we performed the following studies. Serological studies showed the maternal anti-CMV IgG titre tested at delivery to be 1170 U/ml, as determined by enzyme immunoassay; the anti-CMV IgM titre was negative. The infant's anti-CMV IgM titres were negative at birth, but rose to 2·29 U/ml on day 10, indicating a recent CMV infection. Examination of the placenta revealed nonspecific chorioamnionitis and necrotizing funisitis. Foci of plasma cell deciduitis were occasionally observed, but neither vasculitis nor villitis were seen. Thus, a haematogenous transplacental CMV infection seemed unlikely. In situ hybridizaton using a CMV-DNA probe (Enzo Diagnostics. New York, NY) revealed target DNA in scattered decidual cells. Using commercially available CMV glycoprotein-B specific primers (Synthetic Genetics, San Diego, California), the polymerase chain reaction (PCR) was performed. The PCR-amplified products were electrophoresed followed by Southern-blot hybridization analysis with a specific biotinylated probe. Chemiluminescent detection was done using the Smilight kit (Sumitomo-Kinzoku, Co., Japan). Specimens taken from the pharynx on day 0 and urine on day 6 were negative for CMV-DNA. Both specimens were positive for the viral DNA on day 34.

Previous reports of congenital mother-to-infant CMV infection after secondary maternal infection, said to be common in Japan (Chiba *et al.* 1984), did not describe the route of infection, whether haematogenous, ascending, or via the birth canal (Chiba *et al.* 1984; Ahlfors *et al.* 1983; Peckham *et al.* 1983). In our patient, a post-transfusion infection could be excluded, since the infant was positive for anti-CMV IgM before receiving transfusion. The breast milk was a doubtful source of infection, since the period of incubation was too short for seroconversion. Since the infant had been born by caesarean section, transmission through the birth canal also seemed unlikely. We think that CMV had ascended from the vagina via the ruptured membranes to reach the decidua or amniotic fluid; the fetus then aspirated the virus to develop a congenital pneumonia.

We believe this report provides information that will be useful in caring for a CMV seropositive woman whose pregnancy is complicated by preterm prelabour rupture of membranes. The mid-trimester fetus is then placed at risk for a symptomatic CMV infection (Stagno *et al.* 1986).

## Acknowledgment

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# The use of a tissue expansion technique in the reconstruction of the female genitalia in bladder exstrophy

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## Case report

A 23-year-old woman presented with deformity of the external genitalia resulting from bladder exstrophy and scarring due to multiple operations in the pelvis and abdomen.

She had undergone previous surgery to excise the bladder remnant and to provide urinary diversion into an ileal conduit. There had also been several attempts to treat recurrent prolapse of the uterus including uterine suspension with a nylon sling, an anterior colporrhaphy and a gracilis muscle flap. All of these were unsuccessful but repair of the prolapse was eventually achieved using an Ivalon sponge implant. An attempt had also been made to reconstruct the external genitalia using local flaps but it had failed due to a shortage of normal tissue.

The labia majora were absent and the labia minora were deficient (Fig. 1). The clitoris, which had been bifid but was repaired, lay inside the introitus on its anterior aspect. The hair-bearing skin in the pubic area was separated into two halves by a wide vertical scar in the midline. To improve the cosmetic appearance of the external genitalia she underwent further surgery using tissue expansion to provide adequate tissue for reconstruction.

A longitudinal incision was made at the superior border of the hair-bearing skin on each side. Bilateral subcutaneous pockets were dissected beneath the hair-bearing skin and a tissue expander of nominal volume 160 ml and basal measurements 12 × 5 cm was inserted into each. The remote injection valves were located in the subcutaneous tissues on either side of the pelvis. A 50 ml volume of saline was injected into each expander at the conclusion of the procedure, sufficient to fill the dead space between the expander and the enveloping tissue of the subcutaneous pocket.

Following wound healing she attended for weekly injections of an average of 20 ml of saline into each expander. Excessive tension on the skin was avoided to maintain a good blood supply during expansion. After 14 weeks each expander contained 250 ml. Despite the increasing swellings she experienced little discomfort and had been able to continue with her normal activities.

At a second operation (Figs. 2 & 3) a longitudinal incision was made into the expanded skin 2–3 cm from the edge of the vagina on each side. The resulting flaps of skin were everted and sutured to create labial folds and a more slit-like introitus. The upper ends of the flaps were approximated above the clitoris and the clitoris was advanced into a more normal position. An incision was then made at the medial and superior borders of the remaining hair bearing skin and bilateral flaps of this skin were raised. Advancement and rotation were carried out to approximate the flaps in the midline, thus creating a normal pattern of hair distribution (Fig. 4).

Following healing the patient was pleased with the appearance which has been maintained one year following surgery.

## Discussion

Exstrophy of the bladder in females is associated with a complex deformity of the external genitalia (Jones 1973) which interferes with both urinary and sexual function. The labia majora are deficient anteriorly, the clitoris is bifid and the labia minora are poorly developed. The introitus is annular and patulous, and there is distortion of the normal pattern of hair growth on the lower abdomen due to scarring at the site of the excised extrophic bladder. The pubic rami are widely separated and there may be a depression on the lower abdominal wall due to divarication of the rectus abdominis muscles and absence of the symphysis pubis. As a consequence of the bony abnormality and also the deficiency in the pelvic floor muscles the vagina opens too far anteriorly. The appearance is grossly abnormal and is a source of great embarrassment to the patient with consequent reluctance to engage in potential sexual relationships.

Better management of the bladder defect has resulted in an increased life-span of these patients with survival into adult life (Jones 1973); this needs to be matched by adequate recon-

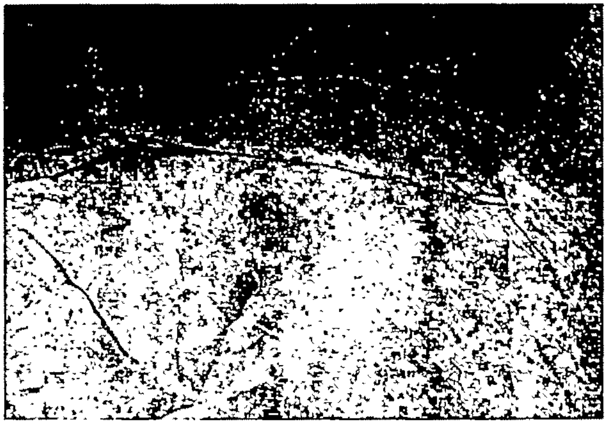

**Fig. 1.** The anterior position of the vagina is shown and above it the midline scarred area of hairless skin.

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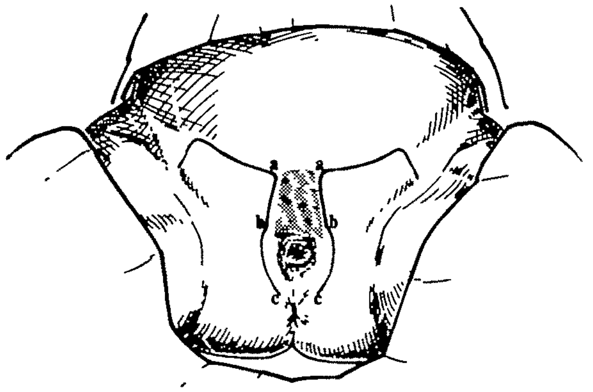

Fig. 2

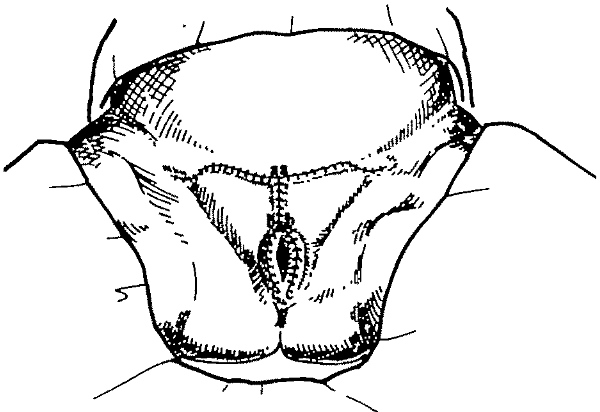

Fig. 3

**Figs. 2 & 3.** Bilateral flaps are planned and raised as shown. After excision of the scarred suprapubic area (Fig. 2, shaded area) the flaps are approximated from 'a-a' to 'b-b' to create a confluent suprapubic area of hair-bearing skin. Along the incisions from 'b' to 'c' the flap edges are everted and sutured to the skin around the introitus to create prominent labial folds.

struction of the external genitalia. Reconstruction should aim at a normal appearance in terms of the shape and pattern of hair growth and of the contours of the genital soft tissues.

Previous methods of repair have relied on inadequate local tissues so that complete reconstruction has not been possible (Erich 1959; Ship 1972; Jones 1973). In particular the labia majora remained deficient leaving the introitus exposed. Tissue expansion overcomes these difficulties by providing an adequate area of skin with suitable characteristics of skin texture, thickness, plasticity, hair growth and sensation.

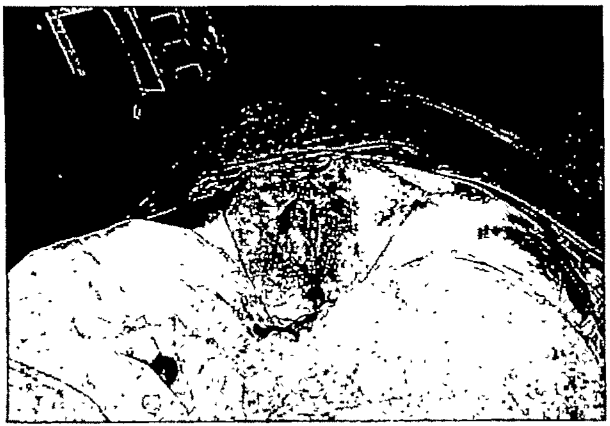

**Fig. 4.** The flaps are sutured in position with good reconstruction of the contours of the perineum and genitalia.

The technique of tissue expansion has been applied successfully in many anatomical areas for the treatment of acquired and congenital defects (Argenta 1984). More specifically, in gynaecological surgery its use has been reported for vaginoplasty (Lilford *et al.* 1988; Johnson *et al.* 1991). The stretching and growth of the skin in response to the expanding silicone balloon is similar to that of the abdominal wall in response to pregnancy and obesity. Additional tissue therefore becomes available for reconstruction at the second stage procedure and, as there is no secondary defect, scarring is reduced. Expanded skin has an increased blood supply which improves the reliability of skin flaps when they are transferred (Cherry *et al.* 1983).

A two-stage procedure is required. The intervening period is necessarily fairly prolonged as it is possible to inject only a limited volume at each visit if excessive tissue tension is to be avoided. A high complication rate (0%–40%) is reported (Argenta 1983; Manders *et al.* 1984), but this can be minimized by careful attention to detail at the time of surgery and by a relatively slow rate of expansion.

The inconvenience to the patient and potential for complications is more than offset by the quality of the reconstruction, which cannot be achieved by any other technique so far described.

## Acknowledgments

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# Endometrial decidual changes in a postmenopausal woman treated with tamoxifen and megestrol acetate

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## Case report

A 41-year-old woman who had had three children attended our outpatient clinic for a routine follow-up. Seven years previously, a right modified, radical mastectomy had been performed for infiltrating duct carcinoma, with metastases to the lymph nodes. Oestrogen and progesterone receptor proteins were positive. Subsequently, she received 6000 rads of irradiation, and six courses of chemotherapy (citofosfan, methotrexate and 5-fluorouracil). Adjuvant tamoxifen therapy (20 mg/day) was instituted. Megestrol acetate was also administered in dosages of 40 mg four times a day.

Menstruation had ceased at the age of 34 following the chemotherapy. Our follow-up procedure involved a transvaginal ultrasound examination of the uterus, and this revealed a hypoechogenic endometrial line of 12 mm thickness and an endometrial polyp. Curettage was performed. On histological examination, the specimen consisted of many fragments of an endometrial polyp with dilated glands and abundant stroma showing decidua-like reaction (Fig. 1). In addition, there was a small fragment of atrophic endometrium with similar decidual changes in the stroma (Fig. 2). The 17-β-oestradiol blood level was 20pg/ml, which is in the normal postmenopausal range.

## Discussion

Tamoxifen acts by binding to the 17-β-oestradiol receptor. Initially, it exerts an oestrogen-like effect, but this is followed by prolonged oestrogen antagonism (Neumannova *et al.* 1985). The antioestrogenic property of tamoxifen on the endometrium is related to its capacity to occupy the oestradiol receptor in the endometrial cells. It has been suggested that tamoxifen exerts its effects on the endometrium via the oestrogen receptor, and that it has a long-term, low-grade oestrogen-like effect (Cross & Ismail 1990; Gusberg 1990). In postmenopausal women with breast cancer, an increase in the karyo-picnotic index indicates oestrogenic changes in the vaginal epithelium (Ferrazzi *et al.* 1977; Boccardo *et al.* 1981), and this is supported by the observations of endometrial hyperplasia (Cross & Ismail 1990), or endometrial polyps (Nuovo *et al.* 1989). Stimulation of endometrial cancer cells in culture by tamoxifen has also been reported (Anzai *et al.* 1989).

Moreover, several groups have observed an increased incidence of endometrial cancer in women with breast cancer and treated with tamoxifen (Killackey *et al.* 1985; Hardell 1988; Fornander *et al.* 1989). Hardell *et al.* (1988) found tamoxifen to be a risk factor for uterine carcinoma, as nearly half of the 23 women with breast cancer in their study who had endometrial

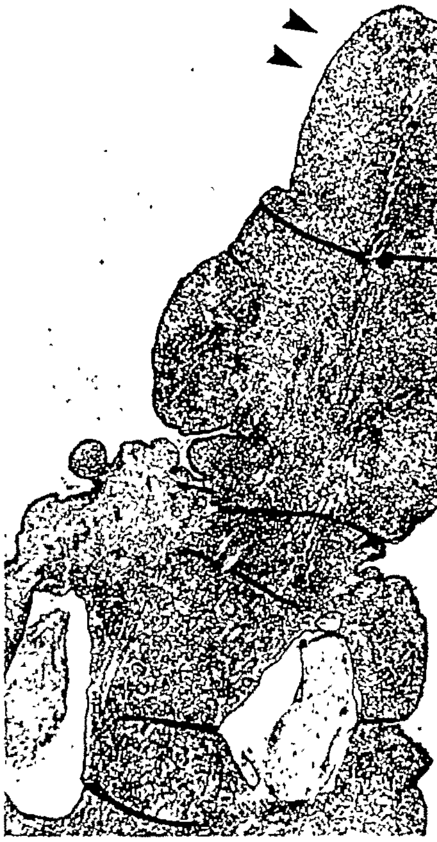

**Fig. 1.** Decidual changes at tip of an endometrial polyp (see arrow) (80 × HE)

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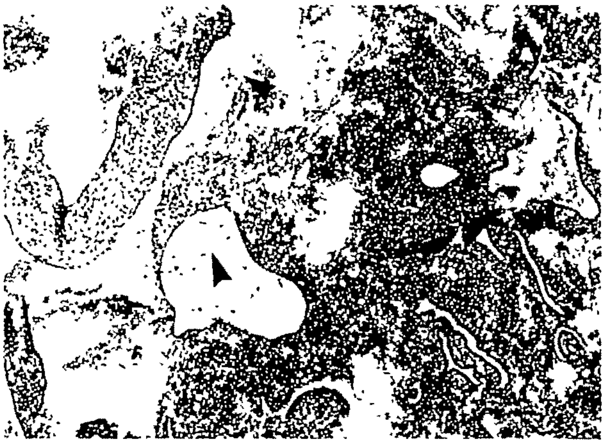

**Fig. 2.** Foci of decidual cells in the endometrial stroma (see arrow) (125 × HE)

cancer were also treated by tamoxifen. A significant increase in the frequency of endometrial carcinoma, in postmenopausal women treated with tamoxifen for breast cancer, has also been reported by Fornander *et al.* (1989).

It is well established that continuous high-dose therapy with progesterone characteristically causes atrophy of glands and a decidual reaction in the stroma (Ober 1966). Such histological changes were also observed in our patient and, to the best of our knowledge, have never before been reported in postmenopausal women treated with tamoxifen and progestogen. It has also been shown that most biological responses to progesterone require prior exposure to oestrogen (Tseng & Gurpide 1975). Oestrogen increases target tissue responsiveness to itself and to progestogens by increasing the concentration of both its own receptor and the intracellular receptors for progesterone (Speroff *et al.* 1989). The ability of different oestrogens to induce progesterone receptor synthesis is proportional to their binding affinity to the oestrogen receptor (Leavitt *et al.* 1977). Moreover, tamoxifen has been shown to induce progesterone receptors (Horowitz *et al.* 1978; Zaino *et al.* 1985).

The histological changes that occurred in our patient, who was treated with tamoxifen and megestrol acetate, can be explained by the above biological mechanisms. The endometrial polyp may have resulted from the prolonged oestrogen-like effect of tamoxifen, while the foci of decidualization in the polyp and in the endometrium probably developed in response to the combined effects of the oestrogen-like effect of the tamoxifen and the progestogen.

The progestational effect described in our patient may protect the endometrium from oestrogen-like changes caused by tamoxifen treatment. There is a need to investigate whether the addition of a progestogen to the tamoxifen treatment regimen in women with breast cancer would reduce the chances for the development of endometrial cancer.

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# Renal cell carcinoma: an unusual cause of second trimester hypertension

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## Case report

A 30-year-old woman in her second pregnancy was noted at her first hospital antenatal clinic visit at 14 weeks gestation to have elevated blood pressure of 150/105 mmHg. Physical examination was otherwise normal with no associated oedema or proteinuria. In her first pregnancy 5 years previously, labour had been induced at 38 weeks gestation because of hypertension and proteinuria (160/100 mmHg and 3+ respectively), at another hospital. She gave birth to a male infant whose weight was on the third centile. Her past medical history was uneventful.

Admission was arranged for assessment of the hypertension. Urine microscopy was normal and culture of a mid-stream specimen showed no growth. Laboratory data included a haemoglobin concentration of 11·9 g/dl with normal red cell indices, a white cell count of 11 × $10^9$/l and a platelet count of 271 × $10^9$/l. The blood urea nitrogen level was normal (1·9 mmol/l) and plasma electrolytes were normal: Na 138 mmol/l, K 3·6 mmol/l and Cl 93 mmol/l. The blood glucose level was normal (3·7 mmol/l). Serum uric acid level was 2·9 mmol/l and the plasma creatinine concentration was 75 μmol/l. Blood pressure readings taken on a 2-h basis subsequently showed a consistently elevated pattern within the range of 140–150/95–105 mmHg. The total protein in a 24-h collection was normal (0·23 g/24 h) as were urinary sodium (177 mmol/24 h), potassium (57 mmol/24 h), urea (304 mmol/24 h) and creatinine (16·1 mmol/l) levels. Creatinine clearance was normal for pregnancy at 149 ml/m and the urinary vanillylmandelic acid was normal at 33 μmol/24 h.

Treatment was started with labetalol 100 mg twice daily on the fourth hospital day and blood pressure readings settled within 48 h to 120–130/75–85 mmHg. She was discharged home on the seventh hospital day. The patient remained normotensive after this time and attended for a routine, detailed fetal ultrasound scan 3 weeks later. During this scan, an 8 to 10 cm mixed echogenic mass was noted in the upper pole of the left maternal kidney suggestive of renal cell carcinoma (Fig. 1). A chest X-ray was normal and blood liver function tests were all within the normal range. A radical left nephrectomy was performed at 19 weeks gestation. The histological picture was that of a renal cell carcinoma and the tumour capsule had not been breached (Fig. 2). The labetalol treatment was discontinued at the time of surgery and the patient remained normotensive throughout the remainder of her pregnancy. She was admitted in early labour at 41 weeks gestation and gave birth spontaneously to a healthy female infant weighing 3440 g. Pathological examination of the placenta revealed no evidence of tumour deposits Computerized tomography 9 months after nephrectomy showed no evidence of recurrent disease.

## Discussion

This case illustrates the diagnostic challenge of the young pregnant patient with a rare disease. Primary renal neoplasms are uncommon in pregnancy and when they occur their presentation is usually quite different to this. Renal cell carcinoma is an adenocarcinoma that arises from the tubular epithelial cells. It may occur at any age but is most common in the sixth decade of life. There is a male to female ratio of 2:1. A review of the literature revealed 71 reported primary renal neoplasms in pregnancy of which 35 (50%) were renal cell carcinomas (Walker & Knight 1986). The most common presenting feature in pregnant patients was a palpable mass (88%). Pain was the second most frequent finding (50%) and haematuria was found in 47% of cases.

Our patient presented with hypertension alone causing a diagnostic dilemma as hypertension is often seen in pregnancy. In view of the clinical findings and laboratory data a diagnostic renal ultrasound scan was not performed during the initial assessment and hence the coincidental finding 3 weeks later.

The low numbers of reported cases of renal cell carcinoma in pregnancy allow few conclusions to be drawn about the effects of pregnancy. There is some evidence that in long-term

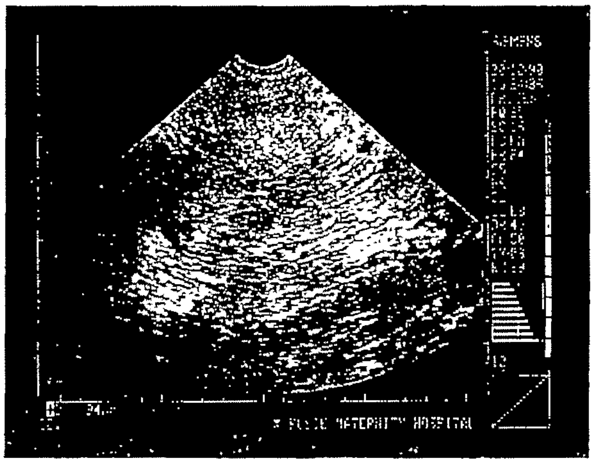

**Fig. 1.** Ultrasound scan of left kidney showing mixed echogenic mass in the upper pole.

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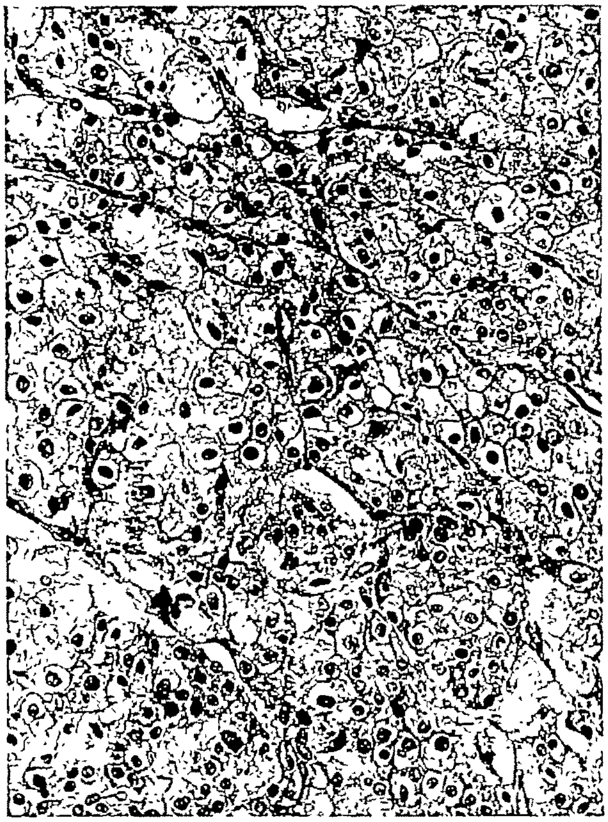

Fig. 2. A view of a section from the tumour showing sheets of tumour cells. There are cells with characteristic clear cytoplasm and areas of granular cytoplasm.

follow up there is a generally better clinical course and survival than would be expected (Ney *et al.* 1971). The increased hormonal levels may have opposite effects, since experimental studies in rodents have reported that oestrogens can cause kidney tumours, while progesterone exerts a protective effect (Bloom *et al.* 1973). Progesterone, for this reason, has been proposed in the treatment of renal cell carcinoma (Concolino *et al.* 1978). The overall effect of the elevated circulating levels of both oestrogen and progesterone is unknown. To our knowledge there have been no cases of fetal metastasis and the effect of future pregnancies on tumour recurrence is unknown.

The recommended treatment for renal cell carcinoma in pregnancy is radical surgical excision. During the first and second trimesters it is not necessary to interrupt the pregnancy to perform radical renal surgery. The situation is generally similar in the third trimester except under circumstances such as severe hypertension, spontaneous tumour rupture, heavy bleeding or difficulty with the trans-abdominal approach to the renal vessels due to uterine size when a caesarean section should be performed.

## Acknowledgments

We would like to thank Mr P. Doyle for allowing us to report this patient. We are grateful to Dr J. Tudor and Dr J. Arno for their help with the ultrasonography and histology, respectively.

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## SHORT COMMUNICATIONS

# Randomized placebo controlled trial to assess the role of intracervical lignocaine in outpatient hysteroscopy

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Outpatient hysteroscopy is now regarded as the investigation of choice for abnormal uterine bleeding as there is no longer any doubt that hysteroscopy is more effective than conventional curettage at identifying intrauterine pathology (Gimpelson, 1984; Goldrath & Sherman, 1985; Gimpelson & Rappold, 1988; Loffer 1989) as it allows direct inspection of the uterine cavity, directed biopsy and appropriate therapeutic management. Another important advantage of hysteroscopy is that it can be performed without general anaesthesia and, in our experience, only 28·5% of patients required local anaesthesia; this was significantly associated with the need to dilate the cervix (Hill *et al.* 1992). In order to assess the role and efficacy of local anaesthesia before hysteroscopy, a randomized placebo controlled double blind trial was performed comparing intracervical lignocaine with saline.

## Subjects and methods

One hundred consecutive women undergoing outpatient hysteroscopy for abnormal uterine bleeding consented to be included in the study; prior support for the study was obtained from the local medical ethics committee. Each patient was randomly allocated to receive either lignocaine 1% or normal saline intracervically. Randomization was performed using a predetermined randomization code in a double blind fashion. Before hysteroscopy, assessments of patient mood, anxiety, presence and severity of lower abdominal and shoulder tip pain were made using a 10 cm visual analogue scale.

The intracervical injection was performed using a 22 French gauge needle through which 10 ml of either lignocaine 1% with 1:200 000 adrenaline or normal saline was injected into the cervix at 1, 5, 7, and 11 o'clock. Hysteroscopy was performed at least 5 min later using a 4 mm HAMOU 1 microcolpohysteroscope with a 30 degree fore-oblique lens and a 5·5 mm diagnostic sheath. The uterine cavity was distended with carbon dioxide via a HAMOU microhysteroflator; illumination was provided by a high intensity cold light source (250 W) via a fibre optic lead (all equipment manufactured by Karl Storz GmbH, Germany). The images were viewed on a high resolution colour monitor using a chip camera. Endometrial biopsies were performed where indicated.

Assessments of both lower abdominal and shoulder tip pain were made using visual analogue scales before, during, immediately after and 30 min after hysteroscopy. The women were also questioned as to whether the hysteroscopy or the intracervical injection was the more painful. The results were statistically analysed using the Mann-Whitney $U$-test and $\chi^2$ test.

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## Results

The median age of the women was 43 (range 25–59) years; 2% were post-menopausal; 16% had never been pregnant and 31% had been sterilized previously. There was no significant difference in any of these characteristics between the lignocaine and saline groups. There was also no difference in the women's mood or anxiety, and occurrence of stomach or shoulder pain prior to hysteroscopy between the two groups.

The indications for hysteroscopy are shown in Fig. 1. Hysteroscopy was unsuccessful in three women: two (one from

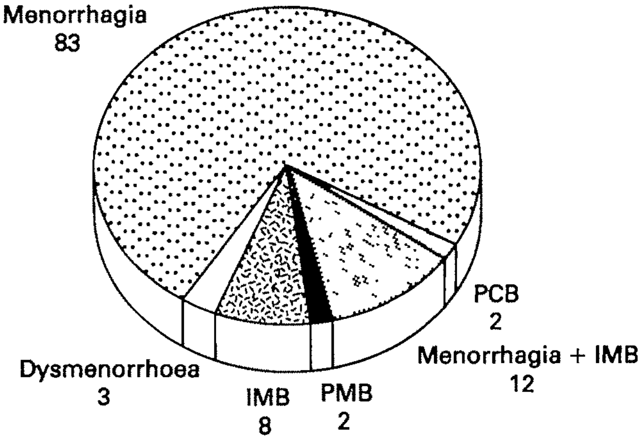

**Fig. 1.** Indications for hysteroscopy. IMB = intermenstrual bleeding; PMB = postmenopausal bleeding; PCB = postcoital bleeding.

**Table 1.** Effect of intracervical lignocaine (lig) or saline (sal) on abdominal and shoulder, tip pain before, during and after hysteroscopy.

| | Before | | During | | After | | 30 min after | |
|---|---|---|---|---|---|---|---|---|
| Degree of pain* | Lig | Sal | Lig | Sal | Lig | Sal | Lig | Sal |
| Abdominal pain | | | | | | | | |
| None | 37 | 36 | 8 | 4 | 14 | 11 | 24 | 21 |
| Mild | 5 | 10 | 20 | 15 | 27 | 26 | 16 | 21 |
| Moderate | 6 | 6 | 14 | 17 | 7 | 10 | 6 | 5 |
| Severe | 2 | 1 | 7 | 12 | 1 | 1 | 3 | 0 |
| Total | 50 | 50 | 49 | 48 | 49 | 48 | 49 | 48 |
| Shoulder tip pain | | | | | | | | |
| None | 48 | 46 | 42 | 43 | 37 | 34 | 42 | 36 |
| Mild | 1 | 3 | 3 | 2 | 5 | 8 | 3 | 6 |
| Moderate | 1 | 1 | 3 | 3 | 4 | 3 | 4 | 6 |
| Severe | 0 | 0 | 1 | 0 | 3 | 3 | 0 | 0 |
| Total | 50 | 50 | 49 | 48 | 49 | 48 | 49 | 48 |

Results are numbers of women.
*Assessed on a 10 cm visual analogue scale.

each group) found the procedure too painful, and one patient fainted after the intracervical injection of saline. These women were excluded from further analysis.

During hysteroscopy, 47 women experienced no, or mild, abdominal pain, 31 moderate and 19 severe abdominal pain, but only 12 had shoulder tip pain (Table 1). There was no significant difference between the incidence of stomach or shoulder tip pain between the women treated with lignocaine or saline. Immediately after hysteroscopy, 53 women had mild pain, but only two severe pain; 26 women had residual shoulder tip pain. There was no difference in these rates between the two groups. Thirty minutes later, 51 women still had some degree of stomach pain and 19 shoulder tip pain, but again these rates were no different between the lignocaine and saline groups. In total, 43% of women found the intracervical injection the most painful part of the procedure and a further 22% found the injection at least as painful as the hysteroscopy.

## Discussion

Approximately one-third of all gynaecological consultations are as a result of abnormal uterine bleeding (Coulter *et al.* 1988) and this proportion rises to almost three-quarters for peri- or post-menopausal patients (Mencaglia *et al.* 1987). Traditionally, over half these patients would have been investigated by dilatation and curettage (Coulter *et al.* 1991), accounting for 26·7% of all gynaecological operative procedures (Mackenzie & Bibby 1978). Out-patient hysteroscopy is now the preferred method of investigation for these patients and more and more hysteroscopies are now being performed without general anaesthesia.

The use of intracervical lignocaine has been shown to be effective as a local anaesthetic when performing procedures on the uterus, such as dilatation and curettage and suction termination of pregnancy. It is surprising, then, to find the results of this study show that there was no statistically significant difference between the two groups with regard to discomfort associated with hysteroscopy. Those women receiving intracervical lignocaine experienced no less discomfort than those receiving saline. This may be a reflection of the type of analgesia used. The sensory nerve supply of the uterus is derived from Frankenhauer's plexus (parasympathetic S2-4) which supplies the cervix and the lower portion of the uterus; however, the fundal region derives its sensory innervation from the ovarian nerve plexus. Therefore, intracervical lignocaine will be effective in reducing the sensitivity of the cervix but will be ineffective at blocking fundal innervation of the uterus. It is possible that paracervical block, either alone or in conjunction with intracervical block, will be a more effective anaesthetic for hysteroscopy, although this was found not to be the case with laser ablation of the cervical transformation zone (Johnson *et al.* 1989).

Another aspect highlighted by this study is the fact that the majority of patients (65%) found the intracervical injection either more, or as painful, as the hysteroscopy. This in itself raises the question of 'who are we treating?', the patient or the physician. It soon became apparent to those conducting the study that the administration of the intracervical injection, whether lignocaine or saline, was itself a painful procedure. In fact, with one patient the procedure had to be abandoned as she fainted following injection of saline. It may well be that administration of anaesthetic solution through a narrower bore needle, such as with dental syringe, may be better tolerated but this needs to be assessed. It would, therefore, appear that the routine administration of intracervical lignocaine is not only ineffective as pain relief during hysteroscopy but can also be counter-productive. We would advocate the use of this form of local anaesthesia in cases where cervical dilatation is required and not as a routine.

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# Histological sampling of the endometrium—A comparison between formal curettage and the Pipelle sampler

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Outpatient endometrial sampling using a Pipelle sampler (Cornier 1984) has been shown to be an acceptable technique, comparing favourably with the Vabra aspirator (Kaunitz *et al.* 1988; Eddowes *et al.* 1990). These studies have compared alternative out-patient methods but they have not assessed the accuracy of the diagnosis obtained by the sampler compared with traditional dilatation and curettage (D & C), which was the objective of our study.

## Subjects and methods

One hundred eighty-seven patients (age range 35–84 years) who had been admitted for dilatation and curettage under general anaesthesia, and who had not previously had out-patient endometrial sampling, were included in the study. They were prepared in the usual manner for D & C, but immediately before the procedure, a Pipelle sampler (Prodimed, Neuilly-en-Thelle, France) was used. The D & C was then performed in the normal way. The Pipelle samples were not submitted with the curettings but were labelled with a hospital number only and examined in batches on a separate occasion to ensure 'blind' assessment. All the samples were examined by one histopathologist (A.S.H.). The amount of tissue obtained by each method was not assessed quantitatively.

Samples were obtained with Pipelles from 171 women and by curettage in 138 women. In two of the 171, the Pipelle provided some tissue but was insufficient to allow a diagnosis.

## Results

In 138 cases, the reports on both sampling procedures were identical, except that in 12 of them curettage identified benign polyps which the Pipelle sampler would not have been expected to detect. The four cases of carcinoma were detected by both methods. In a further 26 cases, one of the procedures yielded no tissue and the other yielded material reported as blood, mucus, or atrophic or endocervical tissue. Thus, in 164 out of 187 women, the two techniques were regarded as providing the same results.

Table 1 compares the histological findings in the 23 discrepant cases. In 11 cases, simple hyperplasia or atypia was reported in the Pipelle sample but either there were no curettings or they were normal. We think that the foci of abnormality were small and preferentially removed by the first sampling procedure. They may, therefore, have been detected by curettage if that had been the first procedure. No cases of atypia or carcinoma were missed by the Pipelle.

In six women, the Pipelle samples showed normal proliferative endometrium, but foci of hyperplasia were seen in the curettings. Three perimenopausal women with irregular bleeding had fragments of proliferative endometrium on curettage, but the Pipelle sample was inadequate for diagnosis in one and no tissue was obtained in the other two. The discrepancy in the histology was inconsequential in the management of these nine

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**Table 1.** Histology of curettings compared with Pipelle samples in the 23 cases in which the reports differed.

| Pipelle: | Normal | Hyperplasia | Atypia | Atrophic | No endometrium | Inadequate | Total |
|---|---|---|---|---|---|---|---|
| Curettage | | | | | | | |
| Normal | | 3 | 2 | 1 | 1 | 1 | 8 |
| Hyperplasia | 6 | | | | | | 6 |
| Atypia | | | | | | | 0 |
| Atrophic | 1 | | | | | | 1 |
| No endometrium | 1 | 5 | 1 | | | 1 | 8 |
| Total | 8 | 8 | 3 | 1 | 1 | 2 | 23 |

women, progestogens were prescribed because of prolonged, irregular cycles.

In the 62 women who had curettage performed for postmenopausal bleeding, a sample was obtained by the Pipelle in every case in which tissue was obtained by curettage; if the Pipelle failed to yield any tissue, then curettage did not yield any tissue either.

## Discussion

The study was devised to determine whether a substantial number of D & Cs could be avoided by Pipelle sampling performed at the patients' initial attendance at the outpatient clinic. We suggest that for women complaining of a menstrual disturbance for whom a D & C would traditionally be considered, the ideal management is to take a Pipelle sample at their first attendance (if they are not bleeding), and then to perform outpatient hysteroscopy at a later date to ensure that there are no endometrial polyps which may be missed even at D & C (MacKenzie & Bibby 1978). Although this study was carried out on anaesthetised patients, it is our experience, and that of others, that sampling with the Pipelle is an easy outpatient procedure that can be performed with minimal discomfort in most women (Eddowes *et al.* 1990). We expect that in our hospital such a policy would save more than 600 D & C procedures annually. Two thirds of the curettages performed for postmenopausal bleeding yielded no tissue, yet these women may have been at considerable risk from a general anaesthetic. A further prospective study is now under way to assess this approach in postmenopausal women.

## Acknowledgments

We would like to thank Unimar and Eurosurgical Ltd for supplying the Fipelle suction curettes, and for financial assistance to cover the additional histopathology. We are also grateful to all our colleagues for their assistance in obtaining samples.

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# CORRESPONDENCE

## Prenatal microbiological risk factors associated with preterm birth

Dear Sir,

I read with interest the article by McDonald regarding microbiological risk factors and preterm birth. The underlying trigger mechanisms for 'idiopathic' preterm labour and the resultant epidemiological, clinical and laboratory investigations to elucidate them resemble the quest for an obstetric holy grail.

Given the generally high prevalence of many of the micro-organisms implicated in preterm delivery not all carriers are destined to deliver preterm. Screening for these organisms in early pregnancy would have a low positive predictive value. However, the prediction of those carriers who *will* deliver preterm remains the crucial to any subsequent interventional strategies. Opening of the cervical os occurs by 32 weeks in one-third of primigravidae (Anderson & Turnbull 1969) and it is possibly in this group of women that cervical dilatation allows ascent through the cervix, subsequent phospholipase release, prostaglandin production and preterm labour. Preterm labour associated with chorioamnionitis is associated with very high levels of $PGE_2$ production by the amnion and choriodecidua, although uncomplicated preterm labour appears to start and progress with relatively low levels (Lopez-Bernal *et al.* 1989). Therefore, alternate mechanisms for the initiation of labour would seem more likely.

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### Authors' reply

Dear Sir,

We agree with the comments expressed by Dr Mike Divers in his letter regarding microbiological risk factors and preterm birth, and appreciate his interest in our work. Several mechanisms have now been postulated as triggers for idiopathic preterm labour, and if we have thrown light on one of these we will be content.

It was never our contention that by screening alone we could predict women who would deliver preterm We have, however, shown that women with heavy carriage of *Gardnerella vaginalis* or *Ureaplasma urealyticum* during the midtrimester have a significantly higher risk of preterm birth. These observations provide a basis for further investigating the nature of the association of these organisms in those women who deliver preterm.

**Helen McDonald**
**On behalf of the authors**

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## Breech delivery and epidural analgesia

Dear Sir,

We were interested to read the recent article by Chada *et al.* (1992). The finding of an increased likelihood of caesarean section in the second stage in primiparae is not surprising, since there is an understandable apprehension to proceed with a breech delivery in such cases. There is no doubt that where the singleton breech is arrested at or above the level of the spines an abdominal delivery would be prudent. However, it has been suggested that when the breech with extended legs is arrested at the pelvic floor, delivery may be assisted by groin traction (Lewis & Chamberlain, 1990). Such traction may however cause femoral fractures and bruising if the force used is excessive or applied in the wrong direction. May (1974) advocated the use of a single blade of Neville Barnes forceps applied in the hollow of the sacrum behind the posterior buttock, to facilitate lateral flexion and a finger inserted into the groin to exert simultaneous traction in order to effect delivery.

In our unit, since 1972, we have used adjustable forceps to deliver 18 primigravidae and 16 multiparae, under caudal or epidural analgesia, in whom the extended breech was arrested at or below the spines. The forceps blades are applied to the bi-trochanteric diameter of the fetal pelvis. The anterior blade may be applied directly to the anterior trochanter or wandered over the sacrum into this position. The posterior blade is applied directly, in the hollow of the sacrum, to the posterior trochanter. Obstetric cream is applied only to the external surface of the blades. After adjusting the grasp of the blades, gentle traction is applied in the appropriate direction while getting the mother to bear down during uterine contractions. If the breech advances easily, the delivery is continued and the blades are removed when the posterior buttock bulges at the perineum. If the breech does not advance easily, or the blades slip off the breech, vaginal delivery is abandoned in favour of caesarean section.

Such deliveries have only been undertaken when there has been no evidence of fetopelvic disproportion, clinically and radiologically, and the estimated fetal weight has been 3·5 kg or less. Since 1980, ultrasound has been used routinely to estimate fetal weight. Of the 34 deliveries so performed, there has been no fetal mortality or significant morbidity but it must be stressed that these procedures have been carried out personally, or supervised closely by one of us (A.S.M.), in the operating theatre with all preparations made to proceed to immediate caesarean section in the event of any difficulty.

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## Breech delivery and epidural analgesia

Dear Sir,

This paper (Chadha *et al.* 1992) is a retrospective chart review of 1456 women with breech deliveries at one centre. We have several concerns with the conclusions drawn from this study.

Firstly, as with all retrospective reviews, there is no control group and there are no clearly defined criteria for inclusion in the epidural or non-epidural groups. Thus, the reasons for some patients receiving an epidural, and others not, are not discussed. This, as briefly outlined in the discussion, may have a major influence on the course of labour. Recent literature suggests that subjective pain experience, in early or latent stages of labour, are predictive of the duration of the latent and active phase, as well as predictive of obstetrical complications (Wuitchik *et al.* 1990). Patients who receive epidurals early in labour from choice may, therefore, have a different course of labour than those who receive it later.

Secondly, receiving an epidural anaesthetic is assumed to be a standardized procedure in this paper. An epidural is insertion of a catheter into the epidural space. The catheter *per se* does not in any way influence either pain or course of labour. The drugs used, how they are used, and where they are injected make the epidural effective or deleterious. There is no information in this paper about the type of local anaesthetics given to these patients, the concentration, volume and frequency of injection, or whether any other drugs such as opioids were used.

Much has happened in obstetric anaesthesia and analgesia over the last decade. Use of low concentration, high volume epidural injections and infusions of local anaesthetics, with or without addition of opioids, have completely changed the management of epidural analgesia in labour (Matouskova *et al* 1990; Chestnut 1988). It is of interest that only three references in the paper are from the anaesthesia literature. Studd's paper, which concluded that epidurals 'prolong the second stage and increase forceps delivery rates', has been questioned by many other authors (Doughty 1969; Walton & Reynolds 1984). The authors state that the 'use of epidural analgesia results in a significant decrease in uterine contraction intensity during the active phase and the second stage of labour' quoting Johnson *et al.* 1972. Johnson's paper deals with a completely different method of anaesthesia to that which is in normal practice today. Johnson's patients went through the whole first stage of labour without analgesia. After full dilatation of the cervix, the patient was given a spinal, or peridural caudal anaesthetic using a large volume of 1% Lidocaine, 15–18 ml, resulting in epidural anaesthesia which caused complete pelvic floor paralysis. Modern epidural analgesia does not result in pelvic floor paralysis to this degree, nor does it result in changes in uterine contractility (Brownridge 1988).

The reason for the increase in caesarean section rates here is not clear. The quoted papers do not support this outcome and in the same issue of your Journal, there is a paper discussing differences in patterns of practice amongst obstetricians with regard to using caesarean sections (Guillemette & Fraser 1992). Many factors contribute to the decision to section a particular patient, as has been amply demonstrated in this country by the Consensus Conference on Caesarean Sections. These factors are not discussed in the paper

We consider that the conclusions drawn in this paper are not valid for the current practice of epidural analgesia. Also, the lack of information about the management of the epidurals means that valid conclusions about the effect of epidurals on the course of breech delivery cannot be drawn from this study.

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## Author's reply

Dear Sir,

We thank Professors Smedstad and Morison for their comments and hope this reply will encourage them to reconsider their conclusions.

The technique of administering epidural analgesia at Aberdeen Maternity Hospital is as follows. A slow intravenous infusion of crystalloid is commenced and the patient placed in left lateral decubitus position. A Portex epidural catheter is placed 4 cm into the epidural space through a 16 gauge Tuohy needle inserted at $L_{3-4}$ interspace. A test dose of 3 ml of 0·5% bupivacaine plain is injected via a Millipore filter after negative aspiration for blood or cerebrospinal fluid. Having confirmed no untoward sequelae, a loading dose of 6–10 ml of 0.25% bupivacaine plain is injected A 0·08% bupivacaine infusion (48 ml 0·5% bupivacaine in 250 ml bag of normal saline) is then commenced at 15–20 ml per hour. Blood pressure is checked every min for 5 min, then every five min for 30 min and then every 30 min. The patients are generally able to move their legs but are restricted to the delivery bed. Bolus top-ups of 4–8 ml of 0·25% bupivacaine are used if required. The objective is to provide complete pain relief which is in keeping with the choice of local women. All epidurals are managed by the resident anaesthetist. Midwives in Aberdeen are not allowed to administer top-up injections nor control the infusion rate. Similarly because of the local cultural preferences it is not standard practice to let the epidural wear off in the second stage. These details were left out of the paper in favour of brevity.

Johnson's paper (1972) was published in the early days of the controversy over the degree of motor function impairment with different types of conduction anaesthesia. It is useful in that it summarizes in one paper the effect on uterine activity of different types of conduction anaesthesia, using each patient as her own control. Despite the progress in obstetric anaesthesia since then Bates *et al.* (1985) reported significantly lower uterine activity integral in women with epidural. (In Reference 7 quoted above there is no mention of how uterine contractility was measured, if at all). Furthermore, Thorp *et al.* (1989) in a controlled study designed specifically to analyse the influence of epidural on caesarean section rates for dystocia in nulliparous women showed significantly increased rates in women with epidural analgesia even after correction for selection bias and controlling for confounding variables. Notwithstanding individual assertions, based largely on one's perceived effects of epidural analgesia, at present there is no good evidence that epidurals do not increase operative delivery rates. Though the use of low concentration, high volume epidural injections and infusions may have lowered the instrumental delivery rates (compared to earlier epidural regimes) these are still higher than in patients receiving conventional or no analgesia and there is still much uncertainty about the optimal concentration or infusion rates of bupivacaine. Kay Dickersin's review of available literature attempts to put matters into perspective (Dickersin 1989).

The decision to do a caesarean section involves an interplay of many factors, not all of which are measureable, particularly in a retrospective study. We therefore examined those factors which might have contributed to the decision to do a casarean section and could also be objectively abstracted from the case records (thus minimizing observer bias). Having excluded patients with medical or obstetrical complications from our study we feel that self selection (for pain relief) was the main criteria for patients receiving epidural analgesia. The personal opinion of the medical staff may have influenced this decision but was impossible to quantify. The epidural and non-epidural groups in our study did not show any significant difference for any of the salient features studied except for cervical dilatation at admission. The possible influence of this difference has been alluded to in our discussion.

We reiterate that in the absence of a prospective randomized controlled trial, we have endeavoured to decipher as much as one can from a retrospective study of the possible association between epidural analgesia and breech delivery.

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## ST-waveform analysis of the fetal electrocardiogram could reduce fetal blood sampling

Dear Sir,

I enjoyed the paper showing that ST waveform analysis of the fetal electrocardiogram (FECG) could reduce the load of fetal blood sampling (Johanson *et al.* 1992). We are conducting a trial of prospective monitoring of high risk labours using ST analysis of the FECG (STan, recorder Cinventa AB, Sweden). Monitoring is started as soon in labour as a single helix fetal scalp electrode (Corometrics) can be applied. The consenting and informed women are randomized into two groups: the first are monitored by conventional cardiotocography (CTG) with a Hewlitt Packard 80300A or 8041A and the FECG is concealed from clinicians; the second group are monitored with CTG and FECG ST waveform analysis. In the first group a fetal blood sampling (FBS) is performed as indicated. In the second group an FBS is performed only if the T/QRS ratio is abnormal, i.e. >0·25 (Arulkumaran *et al.* 1990).

In the pilot study there was a ten-fold reduction in the use of FBS when this was performed only when the T/QRS ratio was abnormal. Intrapartum acidosis was detected in only one baby who was in the control (CTG) group with a normal T/QRS ratio. Delivery was expedited by forceps; the cord pH was 7·27 with a base deficit of (11 mmol/l), showing a baby with an acid base balance consistent with the normal T/QRS ratio. In all other cases the T/QRS ratio would have correctly reassured the obstetrician of the normal acid base status of the fetus.

I believe that prospective monitoring of the FECG using ST analysis can reduce fetal blood sampling. Acidosis will not always be detected by a normal T/QRS ratio <0·25, correctly predicts a normal neonatal outcome. The FECG may be a more sensitive indicator of fetal well-being than acid-base status. Our study is continuing.

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## Confined, managed and delivered: the language of obstetrics

Dear Sir,

Hilda Bastian has written an excellent Commentary about language in our speciality. The best term for pregnant women who are making use of the medical services has been the subject of discussion (Thomson 1986; Rada 1986). Although defined in the Chambers Revised English Dictionary as a physician's client, the word 'patient' has come to have connotations of powerlessness and 'the sick role' (Thomson 1986). To some extent the appropriate term depends on the grammatical context in which it is used, but within this restraint many words would be syntactically correct. We therefore asked some current users of the maternity services for their views on how they would like to be addressed or referred to.

The survey was carried out among 100 women (ages 15 to 40 years) attending the Antenatal Clinic at St James's University Hospital in Leeds. Each woman was shown four separate sentences containing a blank space which could be filled in by any of the terms provided—client, consumer, maternant, mother to be, pregnant woman or patient. Within each context they were asked to indicate their strength of preference (0–10) on a linear analogue scale.

The preferred term varied slightly according to context. For example, 'mother to be' achieved the highest mean rating (85%) in the context of an information brochure, while 'pregnant women' scored highest (82%) for an article in a medical journal. On the other hand, 'consumer' and 'client' scored respectively the lowest and next lowest mark in all cases. 'Patient' scored as intermediate in acceptability in all cases. The neologism 'maternant' scored fourth, irrespective of context.

The unpopular terms, client, consumer and maternant, produced not only low mean scores, but also many extreme results. For example, over half of the respondents gave consumer a score of zero, irrespective of context. On the other hand, many women gave the more popular forms extremely good or bad scores. Mother to be and pregnant women each achieved mean scores exceeding 80% in the context of an information brochure or a medical article respectively. However, 2% of women gave these terms a score of zero in response to the same questions—it is impossible to please or not annoy everyone.

People seem to like the slightly softer terms and dislike words reminiscent of the market—client and consumer. While preferring 'pregnant women' in the context of a medical article, 'mother to be' gets much the highest score for an information brochure. No single way of addressing or referring to women during pregnancy wins all-round approval and the attempt to get round this with the new term, maternant, suggested to us by Mr Rupert Fawdry of Milton Keynes, found little favour.

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## Intra-operative blood loss during elective lower segment caesarean section

Dear Sir,

The finding that the average blood loss at the time of the caesarean section was only 487 ml with only two cases where the loss was greater than 1000 ml (Duthie *et al.* 1992) compares favourably with the mean loss of 1100 ml in previous studies. In view of this it is surprising that the authors strongly advocate that cross-matched blood should be available during an elective or emergency caesarean section.

In our unit during October and November 1991, 87 caesarean sections were performed, 21 elective and 66 emergency. Blood was cross-matched for 74 of these but in only one case was transfusion necessary, a case of placental abruption. The cost of cross-matching for caesarean section in a unit delivering 3200 mothers per year is about £10 000. A large number of these requests are outside routine laboratory hours and can interfere with the ability to provide blood speedily for real emergencies. The fact that antenatal patients are screened late in pregnancy for atypical antibodies means that compatible blood can be provided within 10–15 minutes following an abbreviated cross-match and makes the policy of routine cross-matching hard to justify.

In our unit the following recommendations have been adopted. Cross-matching for caesarean section is not routine but a serum sample should be taken from the patient to be stored in Transfusion for use if necessary. Two units of O Rh negative blood are kept in the Delivery Suite and would be available for dire emergencies. Blood is only cross-matched for caesarean section in selected circumstances such as suspected placental abruption, major degree of placenta praevia and for a patient with known atypical red cell antibodies.

We feel that this is a cost effective policy which does not jeopardize patient care, and is in keeping with the guidelines prepared by British Committee for Standards in Haematology (Waters 1991).

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# BOOK REVIEWS

**A Text and Atlas of Intergrated Colposcopy** by Malcolm Anderson, Joe Jordan & Frank Sharp. Chapman & Hall Medical, London, 1992, 235 pages, fully illustrated with colour plates, £70.00.

It is highly likely that anyone attending a colposcopy course in London over the past 15 years has listened to Malcolm Anderson, Joe Jordan, Ann Morse and Frank Sharp. All four are much sought after faculty members on such courses and we are now privileged to see their undoubted knowledge expressed in this new book. Learning colposcopy calls for colour and pattern recognition and lends itself admirably to the use of an atlas, but true understanding of colposcopy stems from a firm appreciation of the underlying histology. Being fully aware of this, the authors have produced a volume which excels with lavish, high quality photomicrographs of tissue and cellular change, colpophotographs and illustrative diagrams accompanied by a clear, concise text. Such a production is normally very expensive but the price has been kept well within bounds. The absence of any references can be criticized but most of the information is timeless and only the occasional unsubstantiated statement stands out for the reader to challenge.

This book will appeal to everyone interested in colposcopy and is a must for any budding colposcopist aspiring to adopt British practices.

**Ian D. Duncan**

**Gynecologic Oncology. Second edition, Volumes 1 & 2** edited by Malcolm Copplesone, John C. Monaghan, C. Paul Morrow & Martin Tattersall. Churchill Livingstone, Edinburgh 1991, Volume 1 728 pages, Volume 2 731–1497 pages, fully illustrated, £195.00 the set.

This epic second edition of seventeen sections in two volumes aims to satisfy all the needs of general gynaecologists and subspecialists alike. Whilst one hesitates to use the term ‘standard text’, one feels that this may well be a candidate.

The authority is global and largely by well known contributors to their own field. The subject matter is very comprehensive, so much so that an item by item critique is impossible. The breadth of content is to some extent self defeating and one is at times left wondering if certain topics are included for completeness rather than being appropriate. The chapter on ‘Oncological Endocrinology’ typifies this. I feel that descriptions of normal ovarian function etc., are superfluous to a major oncological text and some aspects of tumour endocrinology are duplicated in the sections on ovarian cancer. The initial section on fundamental principles is, however, very important, setting the background to the rest of the book. Given this introduction I found the largely philosophical and dated approach to carcinogenesis strangely out of place amongst the other contributions which generally were readable well referenced and highly appropriate to set the scene for the following sections. One omission that I felt quite obvious was the lack of a more direct approach to molecular biology and molecular genetics, both important new players on the oncological stage. There were sections on molecular biology but within that devoted to viruses and cancer, perhaps the next edition will promote this important topic to a chapter of its own.

The other sections were for the most part appropriate and well presented. I was particularly pleased to see Reconstructive Techniques and Aftercare receiving detailed attention, perhaps a reflection of the increasing awareness of quality of life in cancer care. I felt that a 300 page section devoted to surgical technique seemed somewhat excessive given that these skills are rarely learned from texts although others have published on this before. One sensed yet again that the inclusion of this section was mainly as an act of completion, perhaps surgical techniques would have rested more easily as an appendix or even a companion text.

The same criticism cannot be levelled at the section on diagnostic aids. These have evolved rapidly resulting in a major impact in the diagnosis, assessment and monitoring of gynaecological malignancies. I found this section particularly useful in terms of facts and references yet somewhat light in terms of critical appraisal. The section could well have been rounded off by a critical overview of disease assessment in particular its potential for affecting both quality and quantity of life.

The lack of debate and criticism in favour of dogmatic approach is an ongoing feature of many of the contributions. This may be a criticism of gynaecological oncology itself although the British approach to gynaecological cancer has always been to foster debate and encourage development through it. Such a concept is not universal and I personally feel that global market forces still require black and white rather than grey approaches to the majority of problems within the subspeciality.

If there is such a thing as a standard text in gynaecological oncology then this is it. It has been well edited and referenced and the overall standard of presentation is high. For such a weighty tome it is surprisingly up-to-date and all of the editors must be commended although there are a few areas where the pace of change in a rapidly evolving field has defeated even their best efforts.

The illustrations, diagrams, tables and plates are well used, and clear and also relevant to the text they support. I believe that most readers will find much of value within these 1500 pages. Those with a major interest in cancer will require the use of more up-to-date material in certain areas, yet will not want for background and reference material in these volumes.

**David Luesley**

**Management of Patients with Sexually Transmitted Diseases. Report of a WHO Study. Technical Report Series No 810** World Health Organization, Geneva 1991, 103 pages with figures and tables, SFFr14, US$12.60. Developing countries SwFr9.80.

The authors of this book, the majority of whom work in developing countries, have succeeded in their aim of providing clear guidelines for professionals responsible for improving the care and prevention of sexually transmitted diseases (STDs), particularly at the primary health care level. There is an excellent series of algorithms detailing the management of the common presentations of STDs, according to the level of diagnostic facilities available. Essential advice on continuing evaluation of these protocols at a local level, to take account of changing antibiotic sensitivities and disease prevalences is included. Important elements of STD control such as the diagnosis of HIV infection, counselling, confidentiality, contact slips and instructions on how to use a condom are discussed. The appendices contain details of laboratory techniques and treatment protocols. In the UK, few physicians would use the recommended single dose treatment with benzathine penicillin for primary syphilis, and ceftriaxone, which is recommended for several conditions, is not widely available. This is not intended to be a textbook of STDs, but rather a guide to setting up services. Departments of Obstetrics and Gynaecology would find the ABC of Sexually Transmitted Diseases a more useful ready reference to practice in the UK.

**P. E. Hay**

**Year Book of Obstetrics and Gynaecology 1991**, edited by Daniel R. Mishell, Thomas H. Kirschbaum & C. Paul Morrow. Mosby Year Book 1991, St Louis, Baltimore, London, 570 pages, with figures and tables, £42, $57.95.

Will year books last? They look nice, are pleasant to handle and make a handsome additon to one's shelves. But do we read them or do we just feel comfortable to know they are 'there'? Predicting the demise of printed medical publications and the 'paperless society' the editor of the British Medical Journal (Smith R. (1992) *Br Med J* **304,** 792–793) paints a not-so-futuristic picture of a comprehensive international database providing virtually instant access to scientific material as it appears, obviating the need (or market) for the long-familiar printed medical periodical. Its replacement by the electronic journal with all the advantages of immediacy is already on the horizon.

If 'the end of scientific journals' is indeed in sight it is arguable that review and abstract volume including year books will become more rather than less relevant in order to distil in digestible 'bites' the output of a given year I have never been impressed by the argument that such offerings are invariably out of date by the time they appear (this year book for 1991 deals with material published up to the end of June 1990). Surely an article worth reviewing will remain relevant for at least two or three years. This is a year book with all the best features. It is well bound, beautifully printed, easy to handle and manageable in bed. Its editorship, from the Department of Obstetrics and Gynecology of the University of South California Medical School ensures a high standard of selection and commentary But should we feel wound that out of 437 articles culled from 100 scientific journals oly 65 (15%) emanate from departments in the British Isles? Within that meagre but notable selection our contributions in the fields of fetal medicine, antepartum fetal surveillance and endocrinology/infertility are clearly predominant. In addition to the gamut of obstetrics and gynaecology in 22 chapters (including breast disease) there is a comprehensive review of the place of GnRH agonists in gynaecological practice by Professor Heinrichs of Stanford University Medical Centre in which over half of the 95 preferences relate to work published in 1989 and 1990.

This then is a year book of high quality, reasonably priced (as prices go!) offering a spread of material appropriate to the requirements of clinicians and laboratory workers in our discipline. Whatever the future for the printed scientific word I hope that this year book series will continue in similar vein. Thinning out of the welter of published material may be inevitable but I hope that some journals will never die: after all, where else would this book review see the light of day?

**Alan Amias**

**Critical Care Obstetrics.** Second edition, edited by Steven L Clark, David B. Cotton, Gary D. V. Hankins & Jeffrey P. Phelan. Blackwell Scientific Publications, Boston, Oxford, London, 1991, 733 pages, with figures and tables, £75.

It is a credit to the American subspecialist training system that a book about critical care in obstetrics should be written almost entirely by maternal-fetal medicine subspecialists. In the United Kingdom few obstetricians have clinical experience in obstetric medicine and intensive care. The result is that most feel uneasy about the monitoring and management of critically ill patients. Knowing how to assess and treat and, where appropriate, refer such patients is a prerequisite for improving obstetric care. This book is edited by a group of obstetricians who were pioneers in the field of obstetric intensive care. Their intention is to provide not only a valuable reference but also an up-to-date practical guide to the clinical management of the critically ill pregnant woman. This they have achieved.

The first part of the book, entitled 'Basic Principles', contains an excellent review of cardiorespiratory physiology during pregnancy. Subsequent chapters focus on the techniques and principles of haemodynamic monitoring while assessment of respiratory function and the principles of ventilatory support are sadly neglected. The second and largest part of the book systematically addresses the clinical management of various maternal diseases Hypertension, thrombosis, sepsis, amniotic fluid embolism and other 'standard' conditions are well reviewed but the book also includes valuable chapers on less common problems such as sickle-cell crisis, severe hyperthyroidism, diabetic ketoacidosis, systemic lupus erythematosus, haemolytic-uraemic syndrome, intracranial haemorrhage and abdominal trauma during pregnancy. Each chapter ends with an excellent one page summary of the therapeutic goals, management protocol and appropriate laboratory tests. The two chapters on cardiopulmonary resuscitation and blood and component therapy are worthy additions to the second edition of the book. The final short section, 'Fetal Considerations', is slightly disappointing. Newer ultrasonic methods of assessing fetal well-being are largely ignored and inclusion of a long chapter on fetal echocardiography is of limited interest. The final chapter on the fetal effects of drugs used in critical care is however concise and informative.

I think this book is a worthwhile investment for anyone interested in obstetric medicine and labour ward care. In addition to being a comprehensive reference text, the book contains a lot of useful clinical information which is easily accessible to the reader. As such it would be an appropriate addition to the labour ward shelves. I have no doubt that it would be well read by both obstetricians and anaesthetists

**S. Robson**

## Books received some of which may be reviewed at a later date

**Ethics in Reproductive Medicine** edited by David R. Bromham, Maureen E. Dalton, Jennifer C. Jackson & Peter J. R. Millican. Springer-Verlag, London, Berlin, Heidelberg, 1992, 228 pages, with figures and tables, DM 118.00

**Towards a Healthy Baby. Congenital Disorders and the New Genetics in Primary Health Care** by Bernadette Modell & Michael Modell. Oxford University Press, Oxford, 1992, 411 pages, with figures and tables, £25 00

**Operative Laparoscopy** by Maurice-Antoine Bruhat, Gérard Mage, Jean-Luc Pouly, Hubert Manhes, Michel Canis & Arnaud Wattiez. McGraw-Hill Inc , New York, St Louis, 1992, 288 pages, fully illustrated with colour plates. No price given

**Shoulder Dystocia and Birth Injury: Prevention and Treatment** by James A O'Leary McGraw-Hill, Inc., London, New York, 1992, 234 pages, with figures and tables, $38.00

**Infectious Disease in Pregnancy and the Newborn Infant** edited by Gwendolyn L. Gilbert. Harwood Academic Publishers, Chur, Reading, Paris, Philadelphia, Tokyo, Melbourne, 1992, 618 pages, with figures and tables, $70.00, £38.00 ECU 54.00

**Lasers in Gynaecology. Possibilities and Limitations** edited by G. Bastert & D. Wallwiener in collaboration with D Pollmann & S. Rumbach Springer-Verlag, Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong, Barcelona, Budapest, 1992, 453 pages, with 198 figures, 91 in colour and 105 tables, DM 268.00

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Further information is available upon request from:

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